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(54) Title: NOVEL SUBSTITUTED ARYL COMPOUNDS USEFUL AS MODULATORS OF ACETYLCHOLINE RECEPTORS (57) Abstract <p>In accordance with the present invention, a novel class of substituted aryl compounds (containing ether, ester, amide, ketone or thioether substitution) that promote the release of ligands involved in neurotransmission have been discovered. In a particular aspect, compounds of the present invention are capable of modulating acetylcholine receptors. The compounds of the present invention are capable of displacing one or more acetylcholine receptor ligands, e.g., ³H-nicotine, from mammalian neuronal membrane binding sites. Invention compounds may act as agonists, partial agonists, antagonists or allosteric modulators of acetylcholine receptors. Therapeutic indications for compounds with activity at acetylcholine receptors include diseases of the central nervous system such as Alzheimer's disease and other diseases involving memory loss and/or dementia (including AIDS dementia); cognitive dysfunction (including disorders of attention, focus and concentration), disorders of extrapyramidal motor function such as Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia; mood and emotional disorders such as depression, anxiety and psychosis; substance abuse including withdrawal symptoms and substitution therapy; neurocrine disorders and dysregulation of food intake, including bulimia and anorexia; disorders of nociception and control of pain; autonomic disorders including dysfunction of gastrointestinal motility and function such as inflammatory bowel disease, irritable bowel syndrome, diarrhea, constipation, gastric acid secretion and ulcers; pheochromocytoma, cardiovascular dysfunction including hypertension and cardiac arrhythmias, as well as co-medication uses in surgical applications.</p>		

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Novel Substituted Aryl Compounds
Useful as Modulators of Acetylcholine Receptors

The present invention relates to compounds which potentiate neurotransmission by promoting the release of neurotransmitters such as acetylcholine, dopamine and norepinephrine. More particularly, the present invention relates to compounds that are capable of modulating acetylcholine receptors. Invention compounds are useful, for example, for treatment of dysfunction of the central and autonomic nervous systems (e.g. dementia, cognitive disorders, neurodegenerative disorders, extrapyramidal disorders, convulsive disorders, cardiovascular disorders, endocrine disorders, eating disorders, affective disorders, drug abuse, and the like). In addition, the present invention relates to pharmaceutical compositions containing these compounds, as well as various uses therefor.

BACKGROUND OF THE INVENTION

By modulating neurotransmitter release (including dopamine, norepinephrine, acetylcholine and serotonin) from different brain regions, acetylcholine receptors are involved in the modulation of neuroendocrine function, respiration, mood, motor control and function, focus and attention, concentration, memory and cognition, and the mechanisms of substance abuse. Ligands for acetylcholine receptors have been demonstrated to have effects on attention, cognition, appetite, substance abuse, memory, extrapyramidal function, cardiovascular function, pain and gastrointestinal motility and function. The distribution of acetylcholine receptors that bind nicotine, i.e., nicotinic acetylcholine receptors, is widespread in the brain, including the basal ganglia, limbic system, cerebral cortex and mid- and hind-brain nuclei. In the periphery, the distribution includes muscle, autonomic ganglia, the gastrointestinal tract and the cardiovascular system.

Acetylcholine receptors have been shown to be decreased, *inter alia*, in the brains of patients suffering from Alzheimer's disease or Parkinson's disease, diseases associated with dementia, motor dysfunction and cognitive impairment. Such correlations between acetylcholine receptors and nervous system disorders suggest that compounds that modulate acetylcholine receptors will have beneficial therapeutic effects for many human nervous system disorders. Thus, there is a continuing need for compounds which have the ability to modulate the activity of acetylcholine receptors. In response to such need, the present invention provides a new family of compounds which modulate acetylcholine receptors.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, we have discovered a novel class of substituted aryl compounds (containing an ether, ester, amide, ketone or thioether functionality) that promote the release of ligands involved in neurotransmission. More particularly, compounds of the present invention are capable of modulating acetylcholine receptors.

The compounds of the present invention are capable of displacing one or more acetylcholine receptor ligands, e.g., ³H-nicotine, from mammalian neuronal membrane binding sites. In addition, invention compounds display activity in cell lines which express recombinant acetylcholine receptors. It can readily be seen, therefore, that invention compounds may act as agonists, partial agonists, antagonists or allosteric modulators of acetylcholine receptors. Therapeutic indications for compounds with activity at acetylcholine receptors include diseases of the central nervous system such as Alzheimer's disease and other diseases involving memory loss and/or dementia (including AIDS dementia); cognitive dysfunction

(including disorders of attention, focus and concentration), disorders of extrapyramidal motor function such as Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia; mood and emotional disorders such as depression, anxiety and psychosis; substance abuse including withdrawal symptoms and substitution therapy; neurocrine disorders and dysregulation of food intake, including bulimia and anorexia; disorders of nociception and control of pain; autonomic disorders including dysfunction of gastrointestinal motility and function such as inflammatory bowel disease, irritable bowel syndrome, diarrhea, constipation, gastric acid secretion and ulcers; pheochromocytoma, cardiovascular dysfunction including hypertension and cardiac arrhythmias, as well as co-medication uses in surgical applications.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the effect of saline injection on ACh release in the hippocampus. Saline (1.0 ml/kg) was injected subcutaneously at time = 0 and acetylcholine levels measured as described in Example 7 (n=4 animals).

Figure 2 illustrates acetylcholine release in the hippocampus induced by nicotine. Nicotine (0.4 mg/kg) was injected at time 0, and acetylcholine levels measured as described in Example 7. Statistical significance was determined using students t-test versus saline control animals (*P<0.05, n=4 animals).

Figure 3 illustrates acetylcholine release in the hippocampus induced by lobeline. Lobeline (5.0 mg/kg) was injected at time 0, and acetylcholine levels measured as described in Example 7. Statistical significance was

determined using students t-test versus saline control animals (*P<0.05, n=3 animals).

Figure 4 illustrates acetylcholine release in the hippocampus induced by the compound of Formula Z (as defined hereinafter) wherein A = 4-hydroxyphenyl, B is not present, D = -S-, E = -CH₂CH₂-, and G = 1-methylpyrrolidino. This compound (40 mg/kg) was injected at time 0, and acetylcholine levels measured as described in Example 7. Statistical significance was determined using students t-test versus saline control animals (*P<0.05, n=3 animals).

Figure 5 illustrates acetylcholine release in the hippocampus induced by the above-described compound of Formula Z (closed squares), mecamylamine and the D1 dopamine antagonist, SCH22390 (RBI, Inc., Nadick, MA).

DETAILED DESCRIPTION OF THE INVENTION

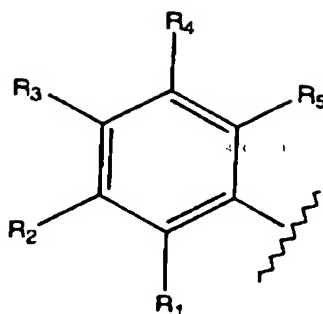
In accordance with the present invention, there are provided compounds having Formula Z, as follows:



or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, wherein:

5

A is



wherein:

each of R_1 , R_2 , R_3 , R_4 and R_5 are independently selected from hydrogen, halogen, cyano, cyanomethyl, nitro, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic, trifluoromethyl, pentafluoroethyl, $-OR_A$, $-O-C(O)-R_A$, $-O-C(O)-N(R_A)_2$, $-SR_A$, $-NHC(O)R_A$ or $-NHSO_2R_A$, wherein R_A is selected from H, lower alkyl, substituted lower alkyl, aryl or substituted aryl, or $-NR_B R_B$, wherein each R_B is independently selected from hydrogen or lower alkyl;

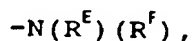
B is optionally present; with the proviso that when B is absent and D is $-O-$, at least one of R_1 , R_2 , R_3 , R_4 or R_5 is not hydrogen, and when B is present, B is selected from lower alkylene, substituted lower alkylene, cycloalkylene, substituted cycloalkylene, lower alkenylene, substituted lower alkenylene, or lower alkynylene;

D is optionally present; and when present is selected from -O-, -C(O)-, -C(O)-NR_c-, -C(O)-O-, -O-C(O)-NR_c-, -S-, -S(O)-, -S(O)-NR_c-, -S(O)₂-, -S(O)₂-NR_c- or -S(O)=NH, wherein R_c is

selected from hydrogen, lower alkyl or substituted lower alkyl;

E is selected from lower alkylene, substituted lower alkylene, lower alkenylene, substituted lower alkenylene or lower alkynylene, with the proviso that when any one of R₁, R₂, R₃, R₄ or R₅ is halogen, nitro, acetamido or cyano, and D is -O-, then E is not methylene;

G is a dialkylamino group having the structure:



wherein:

R^E is hydrogen or a lower alkyl, and

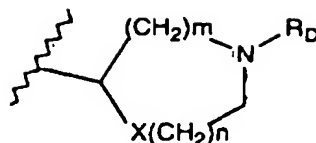
R^F is hydrogen or lower alkyl, or

R^E and R^F combine to form a 3-7 membered ring (with 4-6 membered rings being presently preferred),

with the proviso that when G is dialkylamino, B is absent, D is -O-, and E is C₁₋₃ alkylene, then at least one of R¹ and R⁵ is not alkyl, substituted alkyl, cycloalkyl or substituted cycloalkyl, or

G is a nitrogen-containing cyclic moiety having the structure:

7



as well as bicyclic-derivatives thereof,

wherein:

m is 0-2,

n is 0-3,

5

X is optionally present, and when present is selected from -O-, -CH₂O-, -S-, -CH₂S-, -S(O)-, -CH₂S(O)-, -S(O)₂-, -CH₂S(O)₂- or -CH₂N-, wherein n is not 0 when X is not present, and

10

R₀ is selected from hydrogen, lower alkyl or lower cycloalkyl, or R₀ is absent when the nitrogen atom to which it is attached participates in the formation of a double bond,

with the proviso that:

15

when B is not present, D is -O-, E is a C₁₋₃ alkylene, and G is a nitrogen-containing cyclic moiety wherein X is not present, then m and n combined ≠ 1; and

20

when B is not present, D is -S-, E is -CH₂CH₂-, G is a nitrogen-containing cyclic moiety wherein X is not present, m is zero, n is one and R₀ is CH₃, and each of R₁, R₂, R₄ and R₅ is H, then R₃ is not H, Cl or tert-butyl; and

25

when B is not present, D is -C(O)O-, E is -CH₂-, and G is a nitrogen-containing cyclic moiety wherein X is not present, m is zero, n is one and R₀ is CH₃, then at least one of R₁, R₂, R₃, R₄ and R₅ is not H; and

when B is not present, D is $-C(O)-$, E is a C_{1-3} alkylene, and G is dialkylamino, then R^E and R^F combined are not $-(CH_2)_5-$; and

when B is not present, D is $-C(O)NR_C-$, E is $-CH_2CH_2-$, and G is a nitrogen-containing cyclic moiety wherein X is not present, m is zero, n is 3 and R_D is hydrogen or lower alkyl, then R_1 is not alkoxy, when each of R_2 and R_5 is H, R_3 is NH_2 , and R_4 is halo.

10 Bicyclic derivatives of the above-described nitrogen-containing cyclic moieties include a wide variety of azabicycloalkanes, as described in greater detail hereinbelow.

15 As employed herein, "lower alkyl" refers to straight or branched chain alkyl radicals having in the range of about 1 up to 4 carbon atoms; "alkyl" refers to straight or branched chain alkyl radicals having in the range of about 1 up to 12 carbon atoms; "substituted alkyl" refers to alkyl radicals further bearing one or more
20 substituents such as hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), aryl, heterocyclic, halogen, trifluoromethyl, pentafluoroethyl, cyano, cyanomethyl, nitro, amino, carboxyl, carbamate, sulfonyl, sulfonamide, and the like;

25 "lower alkylene" refers to straight or branched chain alkylene radicals (i.e., divalent alkyl moieties, e.g., methylene) having in the range of about 1 up to 4 carbon atoms; "alkylene" refers to straight or branched chain alkylene radicals having in the range of about 1 up
30 to 12 carbon atoms; and "substituted alkylene" refers to alkylene radicals further bearing one or more substituents as set forth above;

"lower cycloalkyl" refers to cyclic radicals containing 3 or 4 carbon atoms, "substituted lower cycloalkyl" refers to lower cycloalkyl radicals further bearing one or more substituents as set forth above, 5 "cycloalkyl" refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl radicals further bearing one or more substituents as set forth above;

10 "cycloalkylene" refers to cyclic ring-containing divalent radicals containing in the range of about 3 up to 8 carbon atoms (e.g. cyclohexylene), and "substituted cycloalkylene" refers to cycloalkylene radicals further bearing one or more substituents as set forth above;

15 "lower alkenyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon double bond, and having in the range of about 2 up to 4 carbon atoms, and "substituted lower alkenyl" refers to alkenyl radicals further bearing one or more 20 substituents as set forth above;

"alkenyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 25 to 6 carbon atoms presently preferred), and "substituted lower alkenyl" refers to alkenyl radicals further bearing one or more substituents as set forth above;

"lower alkenylene" refers to straight or branched chain alkenylene radicals (i.e., divalent alkenyl moieties, 30 e.g., ethylidene) having at least one carbon-carbon double bond, and having in the range of about 2 up to 4 carbon atoms, and "substituted lower alkenylene" refers to

divalent alkenyl radicals further bearing one or more substituents as set forth above;

"alkenylene" refers to straight or branched chain divalent alkenyl moieties having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms (with divalent alkenyl moieties having in the range of about 2 to 6 carbon atoms presently preferred), and "substituted lower alkenylene" refers to divalent alkenyl radicals further bearing one or more substituents as set forth above;

"lower alkynyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 4 carbon atoms, and "substituted lower alkynyl" refers to alkynyl radicals further bearing one or more substituents as set forth above;

"alkynyl" refers to straight or branched chain hydrocarbonyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 6 carbon atoms presently being preferred), and "substituted alkynyl" refers to alkynyl radicals further bearing one or more substituents as set forth above;

"lower alkenylene" refers to straight or branched chain alkynylene radicals (i.e., divalent alkynyl moieties, e.g., ethynylidene) having at least one carbon-carbon triple bond, and having in the range of about 2 up to 4 carbon atoms, and "substituted lower alkynylene" refers to divalent alkynyl radicals further bearing one or more substituents as set forth above;

"alkynylene" refers to straight or branched chain divalent alkynyl moieties having at least one carbon-carbon

triple bond, and having in the range of about 2 up to 12 carbon atoms (with divalent alkynyl moieties having in the range of about 2 to 6 carbon atoms presently being preferred), and "substituted alkynylene" refers to divalent
5 alkynyl radicals further bearing one or more substituents as set forth above;

"aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms and "substituted aryl" refers to aryl radicals further bearing one or more
10 substituents as set forth above;

"alkylaryl" refers to alkyl-substituted aryl radicals and "substituted alkylaryl" refers to alkylaryl radicals further bearing one or more substituents as set forth above;

15 "arylalkyl" refers to aryl-substituted alkyl radicals and "substituted arylalkyl" refers to arylalkyl radicals further bearing one or more substituents as set forth above;

"arylalkenyl" refers to aryl-substituted alkenyl
20 radicals and "substituted arylalkenyl" refers to arylalkenyl radicals further bearing one or more substituents as set forth above;

"arylalkynyl" refers to aryl-substituted alkynyl radicals and "substituted arylalkynyl" refers to
25 arylalkynyl radicals further bearing one or more substituents as set forth above;

"aroyle" refers to aryl-carbonyl species such as benzoyl and "substituted aroyle" refers to aroyle radicals further bearing one or more substituents as set forth
30 above;

"heterocyclic" refers to cyclic (i.e., ring-containing) radicals containing one or more heteroatoms (e.g., N, O, S) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocyclic" refers to heterocyclic radicals further bearing one or more substituents as set forth above;

"azabicycloalkanes" refers to bicyclic species bearing a nitrogen atom at one of the ring positions. Examples of azabicyclic moieties contemplated for use in the practice of the present invention include 7-azabicyclo[2.2.1]heptane, 8-azabicyclo[3.2.1]octane, 1-azabicyclo[2.2.2]octane, 9-azabicyclo[4.2.1]nonane, and the like; and

"halogen" refers to fluoride, chloride, bromide or iodide radicals.

In accordance with the present invention, A is a phenyl or substituted phenyl moiety, optionally bearing substituents at C₂-C₆ of the phenyl ring. Thus, each of R₁ through R₅ are independently selected from hydrogen, halogen, cyano, cyanomethyl, nitro, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic, perfluoro alkyl (such as, for example, trifluoromethyl, pentafluoroethyl, and the like), -OR_A, -O-C(O)-R_A, -O-C(O)-N(R_A)₂, -SR_A, -NHC(O)R_A or -NHSO₂R_A, wherein R_A is selected from H, lower alkyl, substituted lower alkyl, aryl or substituted aryl, or -NR_BR_B, wherein each R_B is independently selected from hydrogen and lower alkyl, and wherein at least one of R₁, R₂, R₃, R₄ or R₅ is not hydrogen.

Preferred compounds are those in which R_1 through R_5 are each selected from hydrogen, halogen, alkyl, substituted alkyl (including perfluoroalkyl), alkynyl, substituted alkynyl,, $-OR_A$ or $-SR_A$, wherein R_A is selected from H, lower alkyl or aryl, or $-NR_B R_B$, wherein each R_B is independently selected from hydrogen or lower alkyl. More preferably each of R_1 through R_5 are independently selected from hydrogen, lower alkyl, halogen, hydroxyl, hydroxymethyl, alkoxy, amino, and the like.

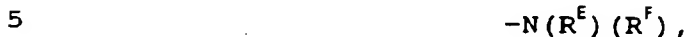
10 In accordance with the present invention, B is selected from straight chain lower alkylene and substituted lower alkylene moieties, or cycloalkylene and substituted cycloalkylene, or lower alkenylene and substituted alkenylene moieties, or lower alkynylene moieties.
15 Presently preferred moieties for B are lower alkylene chains containing 1 to 3 carbon atoms in the backbone thereof.

Further in accordance with the present invention, D is selected from $-O-$, $-C(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, $-S(O)_2-$ or $-C(O)NR_C-$, wherein R_C is selected from hydrogen, lower alkyl or substituted lower alkyl. Preferably D is selected from $-O-$, $-S-$, $-C(O)O-$ or $-S(O)_2-$. It is presently especially preferred that D is selected from $-S-$ or $-C(O)O-$.

25 Still further in accordance with the present invention, E is selected from straight chain lower alkylene and substituted lower alkylene moieties (preferably having up to 3 atoms in the backbone thereof), or lower alkenylene moieties (preferably having about 3 atoms in the backbone thereof), or substituted lower alkenylene moieties and
30 lower alkynylene moieties (preferably having about 3 atoms in the backbone thereof). Presently preferred moieties for E are lower alkylene of 1 to 3 carbon atoms. It is also preferred that when any one of R_1 , R_2 , R_3 , R_4 or R_5 is

halogen, nitro, acetamido or cyano, and D is -O-, then E is not methylene.

Yet still further in accordance with the present invention, G is a dialkylamino group having the structure:



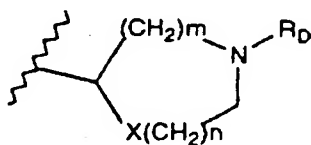
wherein:

R^E is hydrogen or a lower alkyl, and

R^F is hydrogen or lower alkyl, or

10 R^E and R^F combine to form a 3-7 membered ring (with 4-6 membered rings being presently preferred), or

G is a nitrogen-containing cyclic moiety having the structure:



15 as well as bicyclic-derivatives thereof,

wherein:

m is 0-2,

n is 0-3,

20 X is optionally present, and when present is selected from -O-, -CH₂O-, -S-, -CH₂S-, -S(O)-, -CH₂S(O)-, -S(O)₂-, -CH₂S(O)₂- or -CH₂N-, wherein n is not 0 when X is not present, and

R_D is selected from hydrogen, lower alkyl or lower cycloalkyl, or R_D is absent when the

nitrogen atom to which it is attached participates in the formation of a double bond.

Thus, for example, G can be a dialkylamino moiety, an aziridino moiety, azetidino moiety, tetrahydrooxazolo moiety, tetrahydrothiazolo moiety, pyrrolidino moiety, piperidino moiety, morpholino moiety, thiomorpholino moiety, piperazino moiety, an azabicycloalkane, and the like. Presently preferred compounds include those wherein G is an azetidino moiety, pyrrolidino moiety, 1-methylpyrrolidino moiety, 7-azabicyclo[2.2.1]heptane, 8-azabicyclo[3.2.1]octane, 1-azabicyclo[2.2.2]octane, 9-azabicyclo[4.2.1]nonane, and the like.

Preferred compounds of the present invention include those wherein D is -S-; A is 4-hydroxyphenyl, 2-fluoro-4-hydroxyphenyl, 2-chloro-4-hydroxyphenyl or 3-fluoro-4-methoxyphenyl; B is absent; E is lower alkylene; and, G forms a 4-, 5- or 6-membered heterocyclic ring. Particularly preferred compounds of the present invention include those wherein D is -S-; A is 4-hydroxyphenyl, 2-chloro-4-hydroxyphenyl or 3-fluoro-4-methoxyphenyl; B is absent; E is ethylene; and G is pyrrolidino or 1-methylpyrrolidino.

Additional preferred compounds of the present invention include those wherein D is -C(O)O-; A is phenyl, 4-hydroxyphenyl or 4-aminophenyl; B is ethylene or propylene; E is methylene; and G is pyrrolidino or 1-methylpyrrolidino.

Additional preferred compounds of the invention include those wherein D is -S-; B is not present; E is ethylene; G is pyrrolidino; and A is 2-methyl-4-hydroxyphenyl, 4-(NHSO₂-R_A)-phenyl (wherein R_A is -CH₃ or -CF₃), 4-amino (toluenesulfonate)phenyl, 4-methylacetate phenyl, 4-carboxyphenyl, 4-(O-C(O)-N(CH₃)H)phenyl, 4-(CH₂-

NHSO₂-R_A)-phenyl (wherein R_A is lower alkyl, aryl or -CF₃), or 4-(NH-SO₂-N(R_A)₂)phenyl (wherein R_A is lower alkyl, aryl or -CF₃).

Additional preferred compounds of the invention
5 include those wherein D is -O-; B is methylene or not present; E is methylene; G is pyrrolidino; and A is 4-hydroxyphenyl, 4-aminophenyl, or 4-(NHSO₂-R_A)-phenyl (wherein R_A is lower alkyl, aryl or -CF₃).

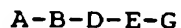
Additional preferred compounds of the invention
10 include those wherein D is -S-; B is methylene or not present; E is methylene; and A is an R-substituted phenyl (wherein R is defined the same as any one of R¹, R², R³, R⁴ or R⁵, e.g., 4-hydroxyphenyl, 4-methoxyphenyl, and the like).

Additional preferred compounds of the invention
15 include those wherein D is -S-; neither B nor E are present; G is 1-methyl-4-piperidino; and A is 4-hydroxyphenyl; as well as compounds wherein D is -S-; B is not present; E is methylene; A is hydroxyphenyl; and G
20 is 7-azabicyclo[2.2.1]heptane, N-methyl 7-azabicyclo[2.2.1]heptane, 8-azabicyclo[3.2.1]octane, N-methyl 8-azabicyclo[3.2.1]octane, 1-azabicyclo[2.2.2]octane, N-methyl 1-azabicyclo[2.2.2]octane, 9-azabicyclo[4.2.1]nonane, or N-methyl 9-azabicyclo[4.2.1]-
25 nonane.

Additional preferred compounds of the invention
include those wherein D is -S-; B is not present; E is -(CH₂)_n-, wherein n = 1-6, e.g., methylene, ethylene, propylene, butylene, and the like; A is 4-hydroxyphenyl;
30 and G is dialkylamino (e.g., dimethylamino), pyrrolidino, piperidino, 7-azabicyclo[2.2.1]heptano, 8-azabicyclo[3.2.1]octano, 1-azabicyclo[2.2.2]octano or 9-azabicyclo[4.2.1]nonano.

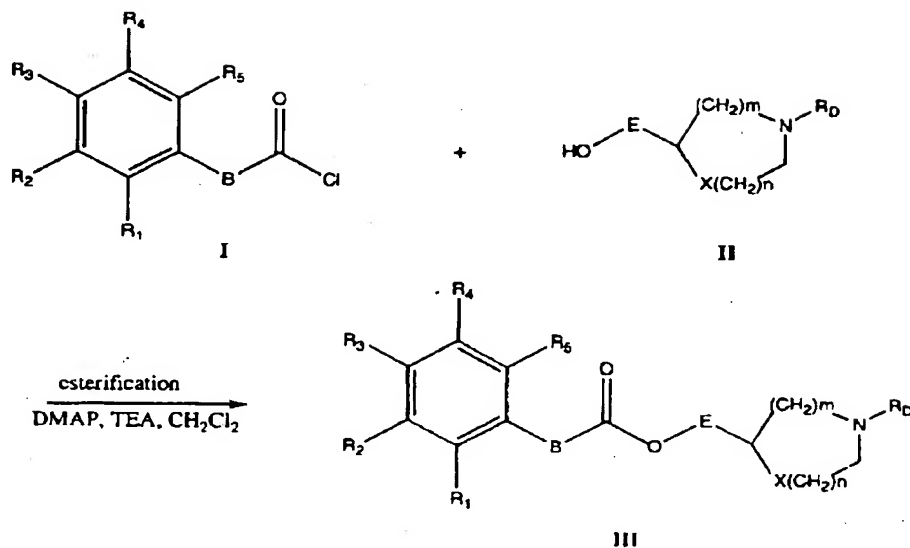
In the following reaction Schemes, each of A, B, D, E and G are as defined above. When any one or more of the R-group substituents of A (i.e., R_1 , R_2 , R_3 , R_4 or R_5) are -OH or -SH, it will be readily apparent to those of skill in the art that this functional group may require the use of "protecting groups" (e.g., t-butyldimethylsilyl (t-BDMS), benzyl (B_n) or tetrahydrophenyl (THP), and the like) during the coupling reaction to "block" the reactivity of the R group. Similarly, when the R-group of A is $-NH_2$, protecting groups (e.g., 9-fluoromethylcarbonyl (Fmoc), butoxycarbonyl (BOC), benzoyloxycarbonyl (CBZ), and the like) may be required. Furthermore, when G = pyrrolidine (i.e., $R_6=H$), an additional protecting step may be required. For such purpose, BOC, CBZ, and the like can be employed. Hence, subsequent deprotection will be required prior to analysis.

Alternative methods for the preparation of compounds having the general Formula Z, as follows:



(Z)

as described herein above, wherein D is present and represents an ester linking moiety (i.e., $-C(O)O-$), are shown in Reaction Schemes I, II and III. In Reaction Scheme I, compounds of Formula I, wherein B is absent or selected from methylene or ethylene, are commercially available and are well known to those of skill in the art. Those compounds not currently available may readily be prepared from starting materials well-known to those of skill in the art.

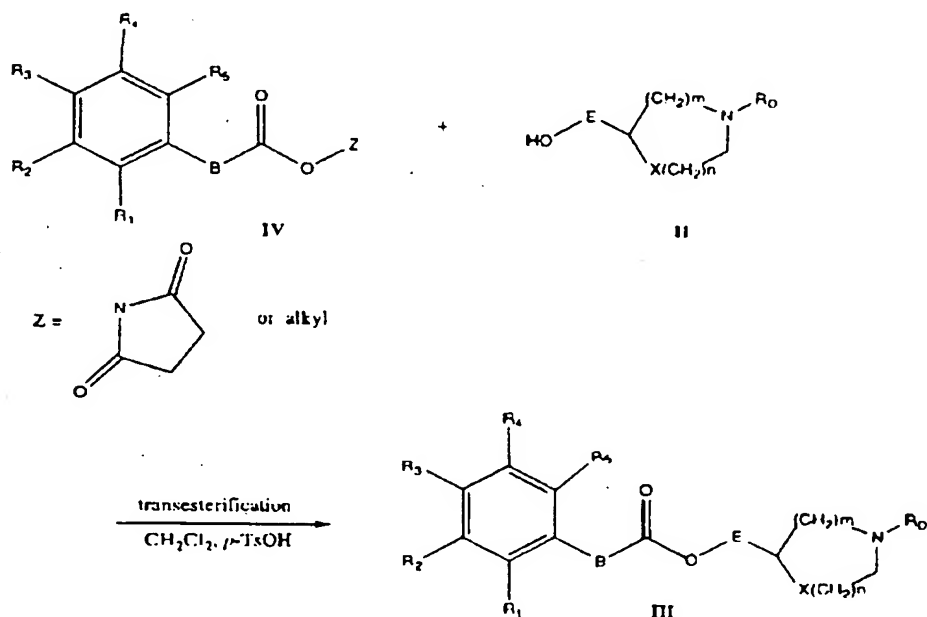
Reaction Scheme I

In Reaction Scheme I, the aryl acid chlorides of Formula I are effectively contacted with the primary alcohol compounds of Formula II, optionally bearing E, and dimethylaminopyridine (DMAP) under anhydrous conditions in an aprotic solvent, such as, for example, methylene chloride (CH_2Cl_2), tetrahydrofuran (THF), ether, diethyl ether, benzene, toluene, and the like. Compounds of Formula II are commercially available, or can be prepared from readily available starting materials, employing techniques well-known to those of skill in the art. See, for example, Kreug and Reinecke, *J. Org. Chem.* 32:225 (1967); Eremeev et al., *Chem. Heterocycl. Compd.* (English Translation) 22:1039-1044 (1986); Morie et al., *J. Chem. Soc. Perkin Trans. 1*:2565-2570 (1994); Habermehl and Ecsy, *Heterocycles* 7:1027-1032 (1977); and Brown et al., *J. Chem. Soc. Perkin Trans. 1*:2577-2580 (1985)). Similarly, hydroxy derivatives of dialkylamines or azabicycloalkanes can be used instead of compounds of Formula II. The reaction mixtures are stirred for 1 to 16 hr, with 4 hours preferred, at reaction temperatures within the range of $-78^\circ C$ up to ambient, with ambient temperatures presently

preferred. The resulting esters (Formula III) are typically purified, e.g., by chromatography over silica, and the final product analyzed by NMR.

Alternatively, compounds of Formula III may be prepared by the trans-esterification reaction described in Reaction Scheme II.

Reaction Scheme II

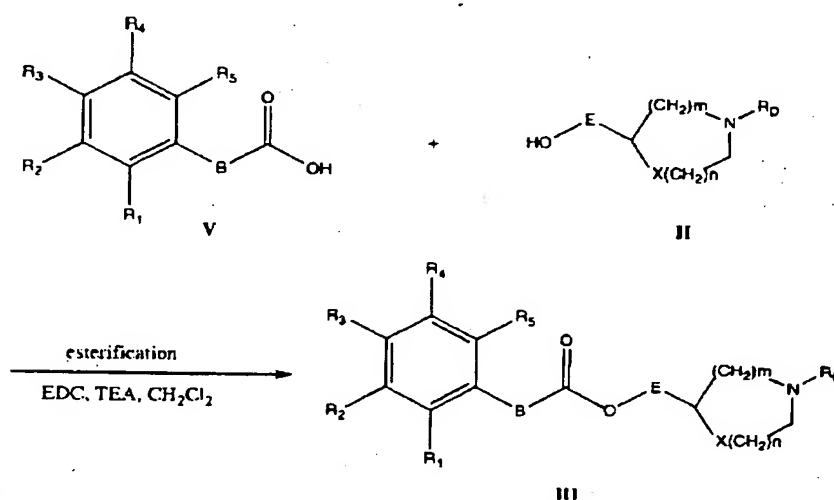


In Reaction Scheme II, aryl esters of Formula IV, optionally containing B, are effectively contacted with compounds of Formula II, optionally bearing E, in the presence of an aprotic solvent (e.g., methylene chloride or benzene) and a catalytic amount of p -toluenesulfonic acid (p -TsOH), to afford the ester compounds of Formula III. Similarly, hydroxy derivatives of dialkylamines or azabicycloalkanes can be used instead of compounds of Formula II. The reaction mixture is refluxed (i.e., boiled) in the range of 8 to 16 hours, with 12 hours

presently preferred, and the resulting ester is purified and analyzed by NMR.

Further, compounds of Formula III may be prepared from aryl carboxylic acid derivatives according to Reaction 5 Scheme III.

Reaction Scheme III



Carboxylic acid derivatives V employed in Reaction Scheme III are commercially available or may readily be prepared from well-known starting materials. Compounds of Formula V are coupled with compounds of Formula II in the presence of triethylamine (TEA), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) in an aprotic solvent such as methylene chloride (CH₂Cl₂) or chloroform and the like. Similarly, hydroxy derivatives of dialkylamines or azabicycloalkanes can be used instead of compounds of Formula II. The reaction mixtures are stirred for 8 to 16 hr, with 12 hr preferred, at reaction temperatures within the range of -78°C to ambient, with

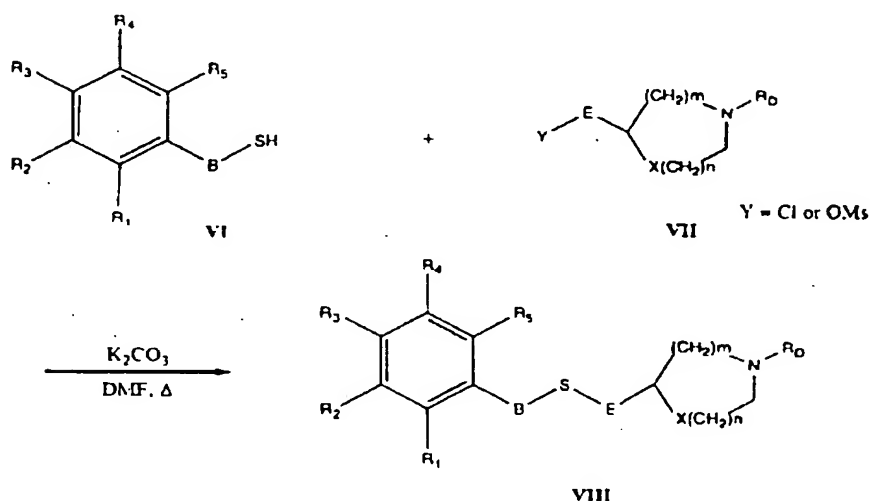
ambient temperatures presently preferred, to afford compounds III. The resulting esters are typically purified by chromatography over silica and the final product analyzed by NMR.

- 5 Reaction Scheme IV illustrates the preparation of compounds having the general Formula Z, as follows:



as described hereinabove, wherein D is a thioether.

Reaction Scheme IV



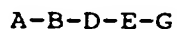
- 10 In reaction Scheme IV the sulfhydryl derivatives of A, and A optionally bearing B, (compounds VI) are commercially available (e.g., thiophenyl, 4-hydroxythiophenyl and 2-phenylethanethiol, Aldrich Chemical Co.) or may readily be prepared by those of skill
- 15 in the art by selecting the appropriate A moiety.

In Reaction Scheme IV, the sulfur compounds (compounds VI) are effectively contacted with the chloride

derivatives of G, optionally bearing E. Compounds VII are commercially available or may be prepared from starting materials well-known to those of skill in the art (see e.g., Wrobel and Hejchman, *Synthesis* 5:452 (1987) or 5 Gautier et al., *Am. Pharm. Fr.* 30:715 (1972)) or, alternatively, the mesylate derivative of compounds II may be used (as prepared according to Fürst and Koller (1947) *Helv. Chim. Acta* 30, 1454). Similarly, chloro or mesylate derivatives of dialkylamines or azabicycloalkanes can be 10 used instead of compounds of Formula VII. This coupling reaction is promoted by suitable base, such as, for example potassium hydroxide, sodium ethoxide, potassium carbonate, 1,8-diazatricyclo[5.4.0]undec-7-ene (DBU), and the like. Presently preferred base for use in the practice of the 15 present invention is potassium carbonate. The above-desired reaction is typically carried out in a solvent such as methanol, tetrahydrofuran (THF), dimethylformamide (DMF), and the like. Presently preferred solvent for use in the practice of the present invention is 20 dimethylformamide (DMF).

Typically the coupling reaction can be carried out over a wide range of temperatures. Temperatures in the range of about 80°C are presently preferred. Reaction times required to effect the desired coupling reaction can 25 vary widely, typically falling in the range of 10 minutes up to about 24 hours. Preferred reaction times fall in the range of about 30 minutes to one hour. The resulting sulfur compound is purified and analyzed by NMR.

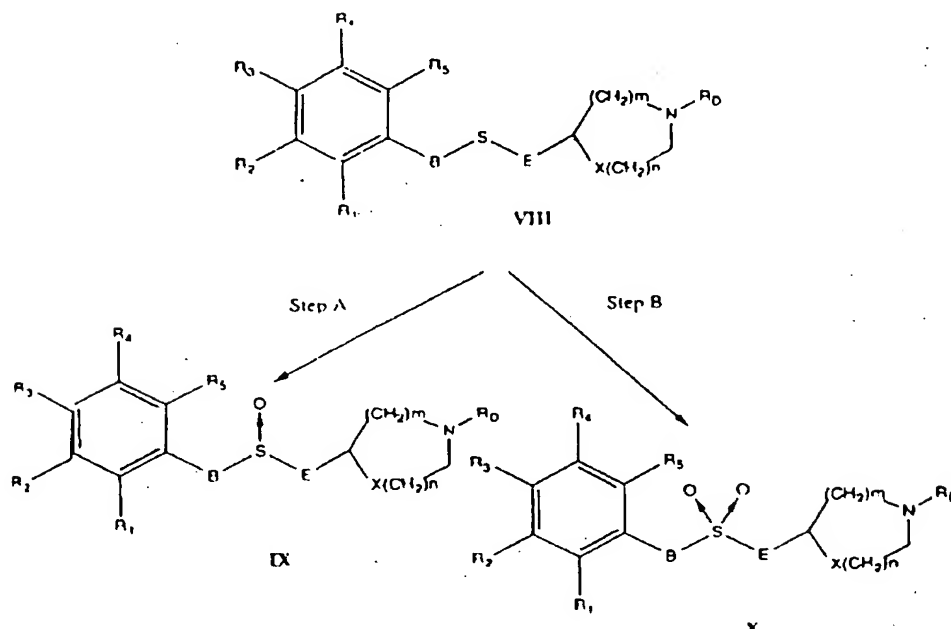
Alternative methods for the preparation of 30 compounds having the general Formula Z, as follows:



(Z)

as described hereinabove, wherein D is present and represents a sulfoxide linking moiety (-S(O)-) or a sulfone linking moiety (-S(O)₂-), are shown in reaction Scheme V.

Reaction Scheme V



- 5 In step A, the resulting thioether derivatives produced, for example, as described in Reaction Scheme IV (compounds VIII), may be oxidized to their corresponding sulfoxides (compounds IX) using about one to about five
- 10 equivalents of a suitable oxidant, such as, for example, hydrogen peroxide, peracids (such as 3-chloroperbenzoic acid), halogen oxide derivatives (such as sodium metaperiodate), N-halogenated derivatives (such as N-bromo or N-chlorosuccidimide), and the like (for a review see M. Madesclaire, *Tetrahedron* 42:5459 (1985)). Presently
- 15 preferred oxidant for use in the practice of the present invention is (about three equivalents of) hydrogen peroxide. The above-described reaction is typically

carried out in a solvent such as methylene chloride, acetic acid, dioxane, ethanol, methanol, and the like. Presently preferred solvent for use in the practice of the present invention is acetic acid.

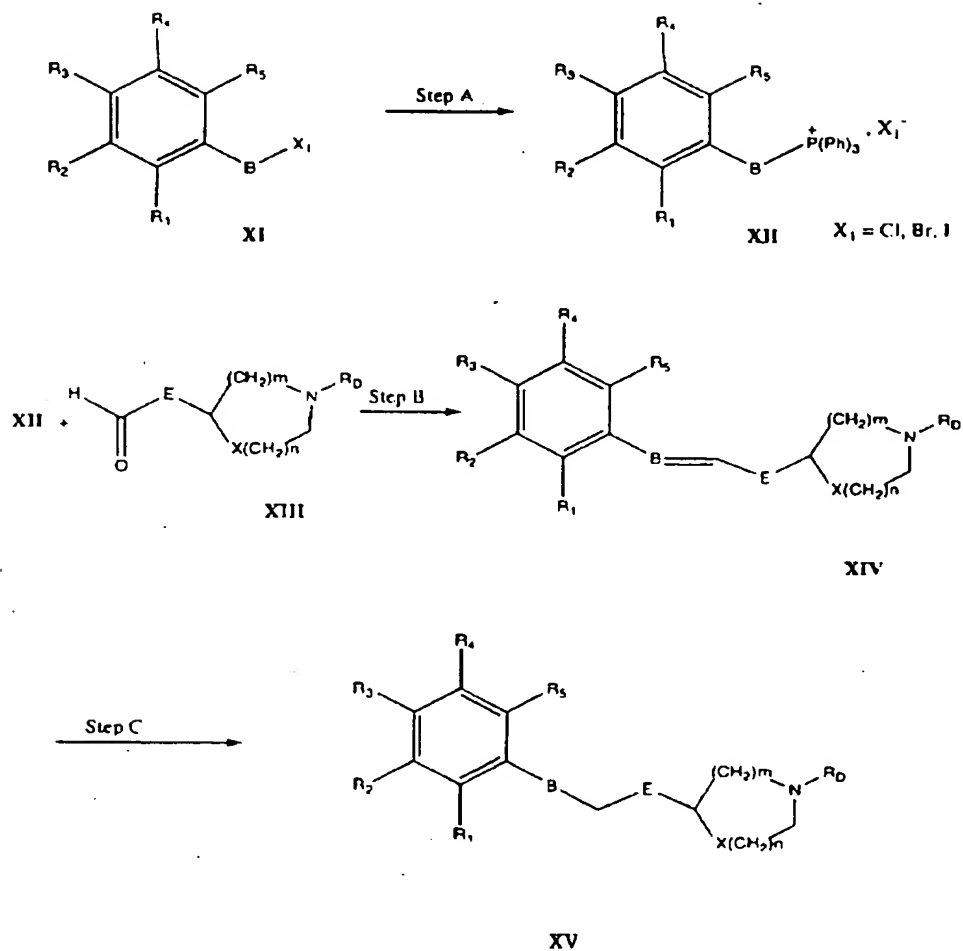
5 Typically the coupling reaction can be carried out over a wide range of temperatures, typically following in the range of about -78°C up to reflux. Temperatures in the range of about 22°C are presently preferred. Reaction times required to effect the desired oxidation reaction can
10 vary widely, typically falling in the range of 10 minutes up to about 24 hours. Preferred reaction times fall in the range of about 30 minutes to one hour. The resulting sulfoxides (compound IX) are purified and analyzed by NMR.

 Alternatively, in step B of Reaction Scheme V,
15 the thioether derivatives (compounds VIII) may be oxidized to their corresponding sulfones (compounds X) using procedures similar to those described above for preparing sulfoxides, but employing elevated levels of oxidant and/or elevated reaction temperatures. In the present invention,
20 hydrogen peroxide in acetic acid under reflux is the preferred condition (R. Gaul et al., *J. Org. Chem.* 26:5103 (1961)). The resulting sulfones (compounds X) are purified and analyzed by NMR.

 Alternative methods for the preparation of
25 compounds having the general Formula Z, as follows:



as described hereinabove, wherein D is not present, are shown in Reaction Scheme VI.

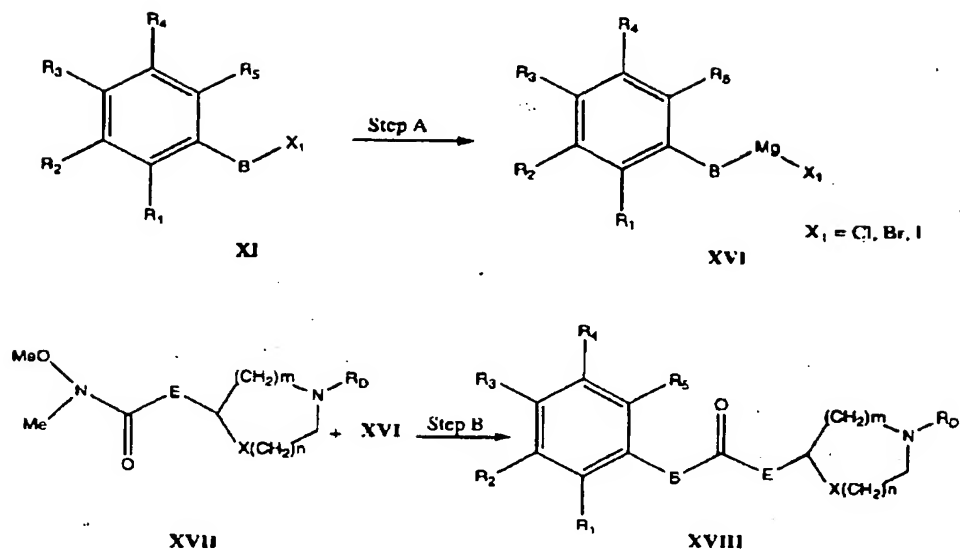
Reaction Scheme VI

As illustrated in Reaction Scheme VI, halogenated derivatives of A (compounds XI), are reacted with triphenyl phosphine in an aprotic solvent such as benzene, toluene, acetonitrile and the like, forming the corresponding phosphonium salts (compounds XII). Typically this reaction may be carried out over a wide range of temperatures. Temperatures in the range of about 80°C are presently preferred. Reaction times required to effect the desired coupling reaction can vary widely, typically falling in the range of 10 minutes up to about 24 hours. Preferred reaction times fall in the range of 12 hours. The resulting compounds are purified and analyzed by NMR.

In Step B of Reaction Scheme VI, the phosphonium salts (compounds XII) are alternatively contacted with an appropriate aldehyde (e.g., compounds XIII, optionally bearing B, or aldehyde derivatives of azabicycloalkanes),
5 via a Wittig reaction well-known to those of skill in the art to afford compounds XIV. Compounds XIII are commercially available or can be readily prepared by oxidation of the corresponding alcohol (i.e., compounds of Formula II, see Reaction Scheme I).

10 In Step C of Reaction Scheme VI, the resulting alkenylene-linker derivatives (compounds XIV) may be reduced to their corresponding saturated alkylene derivatives using procedures well known to those of skill in the art, such as exposure to hydrogen using a Pd/C
15 catalyst.

Alternative methods for the preparation of compounds wherein D is a ketone (i.e., -C(O)-) are shown in Reaction Schemes VII and VIII.

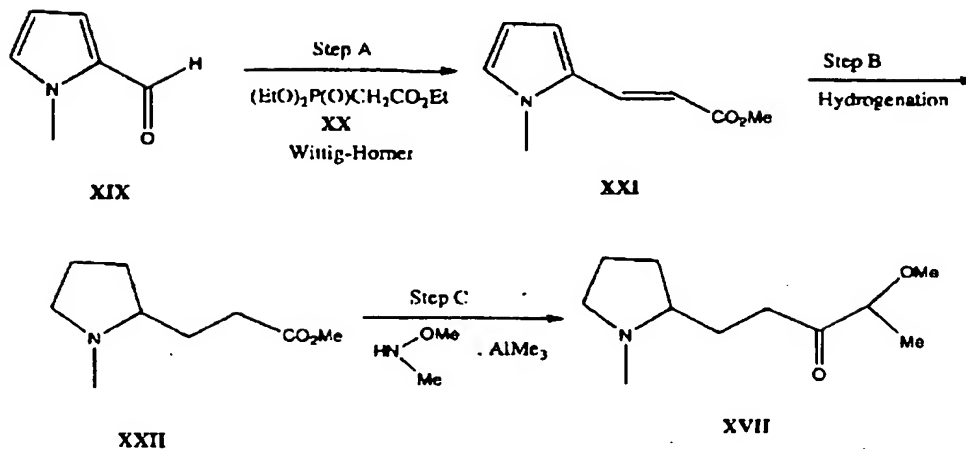
Reaction Scheme VII

As illustrated in Step A of Reaction Scheme VII, halogenated derivatives of A, optionally bearing B (compounds XI) are commercially available (e.g., phenylchloride, Aldrich Chemical Co.), or may readily be prepared by those of skill in the art, are reacted with magnesium in an aprotic solvent such as ether, tetrahydrofuran, benzene and the like, forming the corresponding Grignard reagent (compounds XVI). Presently preferred solvent for use in the practice of the present invention is tetrahydrofuran. Typically this reaction may be carried out over a wide range of temperatures. Temperatures in the range of about 65°C are presently

preferred. Reaction times required to effect the desired reaction can vary widely, typically falling in the range of one hour to about 12 hours. Preferred reaction times fall in the range of 2 hours.

5 In step B of Reaction Scheme VI, compound XVII
(see Scheme VII) can be contacted with Grignard reagent XVI
to afford ketones XVIII (see S. Nahm and S. Weinreb, *Tet*
lett 22:3815 (1981)). Typically this reaction may be
carried out in an aprotic solvent such as tetrahydrofuran,
10 ether and the like. Presently preferred solvent for use in
the practice of the present invention is tetrahydrofuran.
Typically this reaction may be carried out over a wide
range of temperatures. Temperatures in the range of 0°C
are presently preferred. Reaction times required to effect
15 the desired coupling can vary widely, typically in the
range of one hour. The resulting products are purified and
analyzed by NMR.

A method for the preparation of compounds of
Formula XVII is depicted in Scheme VIII.

Reaction Scheme VIII

In Step A of reaction Scheme VIII, aldehyde XIX is contacted with triethyl phosphonoacetate XX, via a Wittig-Horner reaction well known to those of skill in the art in order to obtain the unsaturated ester (compound XXI).

In step B of reaction Scheme VIII the resulting unsaturated ester (compound XXI) may be reduced to the corresponding saturated ester (compound XXII) using procedures well known to those of skill in the art, such as catalytic hydrogenation using a pressure of hydrogen, a catalyst such as PtO₂ and acetic acid as solvent.

In Step C of the reaction Scheme VIII the saturated ester (compound XXII) is contacted with N-methoxy-N-methylamine in the presence of trimethylaluminum in an aprotic solvent such as benzene in order to form the corresponding amide (compound XVII) (Levin et al., *Synt. Com.* 12:989 (1982)).

In addition to the above-described synthetic procedures, those of skill in the art have access to numerous other synthetic procedures which can be employed

for the preparation of invention compounds. Indeed, the literature is replete with methodologies that can be used for the preparation of starting and/or intermediate compounds which are useful for the preparation of invention compounds (e.g., compounds having Formula II, VI, IX, XI, XIV, XVII, XXII, and the like). Such starting and/or intermediate compounds can then be modified, for example, as described herein, to introduce the necessary substituents to satisfy the requirements of Formula I.

10 In accordance with another embodiment of the present invention, there are provided pharmaceutical compositions comprising substituted aryl compounds as described above, in combination with pharmaceutically acceptable carriers. Optionally, invention compounds can
15 be converted into non-toxic acid addition salts, depending on the substituents thereon. Thus, the above-described compounds (optionally in combination with pharmaceutically acceptable carriers) can be used in the manufacture of a medicament for modulating the activity of acetylcholine
20 receptors.

Pharmaceutically acceptable carriers contemplated for use in the practice of the present invention include carriers suitable for oral, intravenous, subcutaneous, transcutaneous, intramuscular, intracutaneous, inhalation,
25 and the like administration. Administration in the form of creams, lotions, tablets, dispersible powders, granules, syrups, elixirs, sterile aqueous or non-aqueous solutions, suspensions or emulsions, patches, and the like, is contemplated. Also contemplated is single dose
30 administration, sustained release administration (e.g., employing time release formulations, metered delivery, repetitive administration, continuous delivery, and the like), administration in combination with other active ingredients, and the like.

For the preparation of oral liquids, suitable carriers include emulsions, solutions, suspensions, syrups, and the like, optionally containing additives such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents, and the like.

For the preparation of fluids for parenteral administration, suitable carriers include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile water, or some other sterile injectable medium immediately before use.

Invention compounds can optionally be converted into non-toxic acid addition salts. Such salts are generally prepared by reacting the compounds of this invention with a suitable organic or inorganic acid. Representative salts include the hydrochloride, hydrobromide, sulfate, bisulfate, methanesulfonate, acetate, oxalate, valerate, oleate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napsylate, and the like. Such salts can readily be prepared employing methods well known in the art.

In accordance with yet another embodiment of the present invention, there are provided methods of modulating

the activity of acetylcholine receptors, said method comprising:

5 contacting cell-associated acetylcholine
 receptors with a concentration of a pyridine
 compound as described above sufficient to
 modulate the activity of said acetylcholine
 receptors.

 As employed herein, the phrase "modulating the
 activity of acetylcholine receptors" refers to a variety of
10 therapeutic applications, such as the treatment of
 Alzheimer's disease and other disorders involving memory
 loss and/or dementia (including AIDS dementia); cognitive
 dysfunction (including disorders of attention, focus and
 concentration), disorders of extrapyramidal motor function
15 such as Parkinson's disease, progressive supramuscular
 palsy, Huntington's disease, Gilles de la Tourette syndrome
 and tardive dyskinesia; mood and emotional disorders such
 as depression, panic, anxiety and psychosis; substance
 abuse including withdrawal syndromes and substitution
20 therapy; neuroendocrine disorders and dysregulation of food
 intake, including bulimia and anorexia; disorders of
 nociception and control of pain; autonomic disorders
 including dysfunction of gastrointestinal motility and
 function such as inflammatory bowel disease, irritable
25 bowel syndrome, diarrhea, constipation, gastric acid
 secretion and ulcers; pheochromocytoma; cardiovascular
 dysfunction including hypertension and cardiac arrhythmias,
 comedication in surgical procedures, and the like.

 The compounds of the present invention are
30 especially useful for the treatment of Alzheimer's disease
 as well as other types of dementia (including dementia
 associated with AIDS), Parkinson's disease, cognitive
 dysfunction (including disorders of attention, focus and
 concentration), attention deficit syndrome, affective
35 disorders, and for the control of pain. Thus modulation of

the activity of acetylcholine receptors present on or within the cells of a patient suffering from any of the above-described indications will impart a therapeutic effect.

5 As employed herein, the phrase "an effective amount", when used in reference to compounds of the invention, refers to doses of compound sufficient to provide circulating concentrations high enough to impart a beneficial effect on the recipient thereof. Such levels
10 typically fall in the range of about 0.001 up to 100 mg/kg/day; with levels in the range of about 0.05 up to 10 mg/kg/day being preferred.

The invention will now be described in greater detail with reference to the following non-limiting
15 examples. All references cited herein are hereby incorporated by reference.

Example 1

Synthesis of Invention Ester Compounds Via Synthetic Scheme I

20 Formation of ester, Method A:

Into a three-neck, round-bottom flask fitted with an addition funnel, a condenser and flushed with argon was placed compound II, 2 mL/mole of dry methylene chloride, triethylamine (1.1 eq.) and a catalytic amount of
25 dimethylaminopyridine. To this mixture the acylchloride I (1.05 eq.) was added slowly at 0°C. The mixture was allowed to warm to room temperature and the reaction was monitored by thin layer chromatography (TLC). After completion, the reaction mixture was poured into water.
30 The aqueous layer was basified with sodium carbonate and extracted three times with 3-4 mL/mole of methylene chloride. The organic phases were combined, washed with

4-5 mL/mole of brine, dried (MgSO_4) and concentrated under vacuum (15 mm Hg) to give an oil which was purified via chromatography on silica using a gradient of chloroform and methanol as eluant.

5 1-Methyl-2-pyrrolidinemethyl phenethylacetate (Method A):

(s)-(-)-1-Methyl-2-pyrrolidinemethanol (2.00 g, 17.4 mmole), triethylamine (1.93 g, 2.66 mL, 19.1 mmole), dimethylaminopyridine (0.01 g) and phenylacetyl chloride (2.81 g, 2.4 mL, 18.2 mmole) were stirred for 10 min at room temperature, yielding 1.01 g (4.32 mmole, 24%) of the desired compound. ^1H NMR (300 MHz, CD_3Cl) δ 7.28 (m, 5H), 4.07 (m, 2H), 3.65 (s, 1H), 3.02 (m, 1H), 2.45 (m, 1H), 2.35 (m, 3H), 2.29 (m, 1H), 1.85 (m, 1H), 1.7 (m, 2H), 1.55 (m, 2H); ^{13}C NMR (75.5 MHz, CD_3Cl) δ 171.5, 133.9, 129.2, 128.4, 126.9, 67.0, 63.6, 57.6, 41.3, 41.2, 28.2, 22.8.

1-Methyl-2-pyrrolidinemethyl 3-phenylpropionate (Method A):

(s)-(-)-1-Methyl-2-pyrrolidinemethanol (2.00 g, 17.4 mmole), triethylamine (1.93 g, 2.66 mL, 19.1 mmole), dimethyl-aminopyridine (0.01 g) and hydrocinnamoyl chloride (3.06 g, 2.7 mL, 18.2 mmole) were stirred for 10 min at room temperature, yielding 2.16 g (8.73 mmole, 50%) of the desired ester.

1-Methyl-2-pyrrolidinemethyl 3-phenylpropionate was converted to the fumarate salt (1.1 g, 3.03 mmole, 75%). ^1H NMR (300MHz, CD_3OD) δ 7.23 (m, 5H), 6.68 (s, 2H), 4.40 (m, 1H), 4.27 (m, 1H), 3.60 (m, 2H), 3.11 (m, 1H), 2.92 (m, 2H), 2.86 (s, 3H), 2.68 (m, 2H), 2.23 (m, 1H), 2.05 (m, 2H), 1.80 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 174.1, 171.7, 142.2, 136.7, 130.0, 129.9, 127.8, 68.5, 63.2, 58.4, 41.3, 36.8, 32.1, 28.1, 23.5; mp 97-98°C; C H N Analysis $\text{C}_{15}\text{H}_{21}\text{NO}_2$ 1.0 ($\text{C}_4\text{H}_4\text{O}_4$).

Example 2Synthesis of Invention Ester Compounds via
Synthetic Scheme II1-Methyl-2-pyrrolidinemethyl 3-(4-hydroxyphenyl)propionate

5 Into a two neck, round-bottom flask fitted with
a condenser and flushed with nitrogen was placed (S)-(-)-1-
methyl-2-pyrrolidinemethanol (10.4 g, 3.5 mmoles), 3-(4-
tertbutyldimethylsilylhydroxyphenyl propionic acid
N-hydroxysuccinimide ester (1.2 g, 3.18 mmole), a catalytic
10 amount of p-toluenesulfonic acid (0.02 g) and anhydrous
methylene chloride (10 mL). The mixture was refluxed for
12 hours, hydrolyzed with water (20 mL) and extracted with
methylene chloride (3 x 25 mL). The organic layers were
combined, washed with about 50 mL of brine, dried (MgSO₄)
15 and concentrated under vacuum (15 mm Hg). The crude
material was purified via chromatography on silica using
chloroform as eluant yielding 1.13 g of pure material (3.01
mmole, 91%). The alcohol was deprotected using 1.1 eq of
tetrabutylammonium fluoride in THF at room temperature for
20 30 min. After an aqueous work-up, the crude material was
purified via chromatography on silica using
chloroform/methanol (99:1) as eluant yielding 0.33 g of the
desired ester (1.25 mmole, 95%).

¹H NMR (300 MHz, CDCl₃) δ 6.92 (d, J=7Hz, 2H),
25 6.68 (d, J=7Hz, 2H) 4.12 (t, J=7Hz, 2H), 3.14 (m, 1H), 2.78
(m, 2H), 2.50 (m, 3H), 2.45 (s, 3H), 2.31 (m, 1H), 1.80 (m,
4H); ¹³C NMR (75.5 MHz, CD₃OD) δ 173.3, 155.2, 131.3, 129.4,
129.1, 115.6, 115.5, 65.1, 64.2, 57.4, 41.3, 35.9, 29.9,
27.6, 22.3; mp 114-115°C; CHN Analysis: C₁₅H₂₁NO₃.

Example 3Synthesis of Invention Ester Compounds Via
Synthetic Scheme III1-Methyl-2-pyrrolidinemethyl 3-(4-aminophenyl)butanoate:

5 Into a two neck, round bottom flask fitted with
a condenser and flushed with argon was placed (S)-(-)-1-
methyl-2-pyrrolidine methanol (0.16 g, 1.43 mmole), 4-(4-
tertbutyl-carbonylaminophenyl)butyric acid (0.40 g, 1.43
mmole), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
10 as its HCl salt (0.28 g, 1.43 mmole), triethylamine (0.15
g, 0.20 mL, 1.43 mmole), and methylene chloride (15 mL).
The reaction mixture was stirred at room temperature for 12
hours, hydrolyzed with water (20 mL) and extracted with
methylene chloride (3 x 20 mL). The organic layers were
15 combined, washed with 50 mL of brine, dried (MgSO₄) and
concentrated under vacuum (15 mm Hg). The crude material
was purified via chromatography on silica using
chloroform/methanol (99:1) as eluant, giving 0.26 g of the
protected compound (48%). The amine was deprotected by
20 stirring the compound in trifluoroacetic acid (2.5 mL) at
room temperature for one hour. The solvent was removed
under vacuum and the crude material was purified via
chromatography on silica using chloroform/methanol (96:4)
as eluant, yielding to 0.80 g (0.29 mmole, 40%) of the
25 desired ester.

1-methyl-2-pyrrolidinedimethyl 3-(4-
aminophenyl)butanoate (0.80 g, 0.29 mmole) was converted to
the fumarate salt (0.50 g, 0.1 mmole, 34%). ¹H NMR (300 MHz,
CD₃OD) δ 6.81 (d, J=7Hz, 2H), 6.58 (d, J=7Hz, 2H), 6.57 (s,
30 4H), 4.26 (m, 1H), 4.1 (m, 1H), 3.48 (m, 4H), 3.02 (m, 1H),
2.78 (s, 3H), 2.39 (m, 2H) 2.22 (m, 2H), 2.14 (m, 1H), 1.92
(m, 1H), 1.74 (m, 2H); ¹³C NMR (75.5 MHz, CD₃OD) δ 116.4,
172.0, 146.6, 137.9, 135.9, 132.4, 120.0, 70.5, 69.1, 60.2,
43.1, 37.4, 36.0, 29.9., 29.7, 25.3; mp = 65-70°C.

Example 4Synthesis of Invention Thioether Compounds Via
Synthetic Scheme IVFormation of thioether (Method B):

5 Into a two neck flask fitted with a condenser, a
thermometer and flushed with argon was placed 2-(2-
chloroethyl)-1-methylpyrrolidine (1 eq), potassium
carbonate (10 eq) and dry dimethylformamide (2 mL/mole).
The reaction mixture was heated at 70°C for 30 minutes,
10 cooled to room temperature, and poured into 3 mL/mole of
a saturated solution of sodium bicarbonate (4 mL/mole).
The resulting mixture was extracted three times with 4
mL/mole of ethyl acetate. The organic layers were
combined, washed with brine, dried (MgSO₄) and concentrated
15 under vacuum (0.01 mm Hg) to give an oil. The crude
material was purified via chromatography on silica using a
gradient of chloroform and methanol as eluant.

2-(2-Phenylthioethyl)-1-methylpyrrolidine (Method B):

2-(2-Chloroethyl)-1-methylpyrrolidine (1.30 g,
20 0.08 mmole), thiophenol (1.00 g, 9.08 mmole), potassium
carbonate (12.56 g, 90.8 mmole) and DMF (18 mL) were
combined, yielding 1.77 g (8.01 mmole, 89%) of the desired
compound.

2-(2-Phenylthioethyl)-1-methylpyrrolidine (0.12
25 g, 0.54 mmole) was converted to the fumarate salt (0.17 g,
0.51 mmole, 94%). ¹H NMR (300 MHz, CD₃OD) δ 7.40 (m, 2H),
7.29 (m, 2H), 7.22 (m, 2H), 6.67 (s, 2H), 3.62 (m, 1H),
3.40 (m, 1H), 3.12 (m, 2H), 2.95 (m, 1H), 2.81 (s, 3H),
2.35 (m, 1H), 2.21 (m, 3H), 1.8 (m, 2H); ¹³C NMR (75.5 MHz,
30 CD₃OD) δ 171.5, 136.5, 136.3, 131.1, 130.3, 127.8, 68.8,
57.1, 39.5, 31.2, 30.8, 30.3, 22.4; mp 109-111°C; C H N
Analysis C₁₃H₁₉NS 1.0(C₄H₄O₄).

2-[2-(4-Hydroxyphenyl)thioethyl]-1-methylpyrrolidine
(Method B):

2-(2-Chloroethyl)-1-methylpyrrolidine (2.0 g, 13.5 mmole), 4-hydroxythiophenol (1.7 g, 13.5 mmole), potassium carbonate (18.7 g, 135.4 mmole) and DMF (26 mL) were combined, yielding 1.42 g (5.98 mmole, 44%) of the desired compound.

2-[2-(4-Hydroxyphenyl)thioethyl]-1-methylpyrrolidine (0.20 g, 0.84 mmole) was converted to the hydrochloride salt (0.13 g, 0.47 mmole, 56%). ¹H NMR (300 MHz, CD₃OD) δ 7.22 (m, 2H), 6.67 (m, 2H), 3.52 (m, 1H), 3.35 (m, 1H), 3.05 (m, 1H), 2.86 (m, 1H), 2.76 (s, 3H), 2.68 (m, 1H), 2.26 (m, 1H), 1.95 (m, 3H), 1.64 (m, 2H); ¹³C NMR (75.5 MHz, CD₃OD) δ 159.3, 136.0, 124.8, 117.7, 69.5, 57.7, 40.2, 33.8, 31.6, 30.8, 22.9; mp 144-146°C; C H N analysis C₁₃H₁₉NOS.HCl.

2-[2-(3,4-Dichlorophenyl)thioethyl]-1-methylpyrrolidine
(Method B):

2-(2-Chloroethyl)-1-methylpyrrolidine (1.50 g, 10.26 mmole), 3,4-dichlorobenzenethiol (1.82 g, 10.1 mmole), potassium carbonate (14.03 g, 101.6 mmole) and DMF (20 mL) were combined, yielding 0.46 g (4.34 mmole, 43%) of the desired compound.

2-[2-(3,4-Dichlorophenyl)thioethyl]-1-methylpyrrolidine (0.46 g, 1.58 mmole) was converted to the hydrochloride salt 0.36 g (1.10 mmole, 69%). ¹H NMR (300 MHz, CD₃OD) δ 7.45 (m, 1H), 7.38 (m, 1H), 7.22 (m, 1H), 3.54 (m, 1H), 3.35 (m, 1H), 3.05 (m, 2H), 2.90 (m, 1H), 2.78 (s, 3H), 2.30 (m, 1H), 1.78-2.13 (m, 5H); ¹³C NMR (75.5 MHz, CD₃OD) δ 136.7, 132.9, 131.0, 130.6, 130.2, 128.9, 68.1, 56.3, 38.8, 29.9, 29.7, 29.4, 21.4; mp 115-116°C.

2-[2-(3-Fluoro-4-methylphenyl)thioethyl]-1-methylpyrrolidine (Method B):

2-(2-Chloroethyl)-1-methylpyrrolidine (1.4 g, 9.48 mmole), 3-fluoro-4-methoxythiophenol (1.5 g, 9.48 mmole), potassium carbonate (13.1 g, 94.8 mmole) and DMF (20 mL) were combined, yielding 1.90 g (7.03 mmole, 74%) of the desired compound.

2-[2-(3-Fluoro-4-methoxyphenyl)thioethyl]-1-methylpyrrolidine (0.905 g, 3.36 mmole) was converted to the fumarate salt 1.18 g (3.06 mmole, 91%). ¹H NMR (300 MHz, CD₃OD) δ 7.12 (m, 2H), 6.95 (m, 1H), 6.57 (s, 2H), 3.55 (m, 1H), 3.32 (m, 1H), 2.97 (m, 2H), 2.78 (m, 1H), 2.73 (s, 3H), 2.23 (m, 1H), 1.97 (m, 3H), 1.88 (m, 2H); ¹³C NMR (75.5 MHz, CD₃OD) δ 171.11, 153.2 (d, J=20Hz), 148.5 (d, J=10Hz), 135.9, 129.0 (d, J=4Hz), 127.1 (d, J=6Hz), 120.0 (d, J=20Hz), 114.9 (d, J=2Hz), 68.45, 56.7, 56.5, 39.2, 32.36, 30.65, 30.0, 22.1; mp 104-105°C.

2-[2-(2-Chloro-4-hydroxyphenyl)thioethyl]-1-methylpyrrolidine (Method B):

2-(2-Chloroethyl)-1-methylpyrrolidine (2.85 g, 19.29 mmole), 2-chloro-4-hydroxythiophenol (3.1 g, 19.29 mmole), potassium carbonate (26.7 g, 192.9 mmole) and DMF (30 mL) were combined, yielding 3.2 g (11.77 mmole, 61%).

2-[2-(2-Chloro-4-hydroxyphenyl)-thioethyl]-1-methylpyrrolidine (0.575 g, 2.12 mmole) was converted to the fumarate salt (0.34 g, 0.78 mmole, 37%). ¹H NMR (300 MHz, CD₃OD) δ 7.32 (d, J=7Hz, 1H), 6.82 (d, J=2Hz, 1H), 6.64 (dd, J=2Hz and 7 Hz, 1H), 6.59 (s, 1.4H), 3.55 (m, 1H), 3.38 (m, 1H), 3.0 (m, 2H), 2.73 (s, 3H), 2.7 (m, 1H), 2.28 (m, 1H), 1.98 (m, 3H), 1.75 (m, 1H); ¹³C NMR (75.5 MHz, CD₃OD) δ 173.3, 161.7, 140.9, 138.7, 138.1, 124.8, 119.9,

118.0, 70.6, 59.0, 41.4, 34.0, 32.7, 32.1, 24.2; mp 134-135°C; C H N analysis $C_{13}H_{18}ClNOS$ 1.4($C_4H_4O_4$).

Example 5
Radioligand Binding

5 3H -Nicotine binding to rat cerebral membranes was performed according to modifications of the method of Flynn and Mash (*J. Neurochem.* 47:1948 (1986)). 3H -Nicotine (80 ci/mmol; New England Nuclear Corporation, Boston, MA) was used as the ligand for nicotinic acetylcholine receptor
10 binding assays. All other reagents were purchased from the Sigma Chemical Co. (St. Louis, MO).

Male Sprague-Dawley rats (250 - 400 gm) were sacrificed by decapitation, the brains removed and the cerebral cortex dissected on ice. Synaptic membranes were
15 prepared by homogenizing the cortical tissue in 20 volumes of ice-cold modified Tris buffer (50 mM Tris pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM EDTA, 1 mM PMSF) with a polytron (20 sec at setting 5-6) followed by centrifugation (15 min at 25,000 x g) at 4°C. The resultant pellet was rehomogenized
20 and centrifuged twice. The final pellet was resuspended in ice-cold assay buffer (50 mM Tris pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$) at a concentration of membrane equivalent to 1 gm wet weight cortex per 10 ml buffer. After protein determination the final membrane preparation
25 was diluted with buffer to 3 mg protein/ml. This membrane preparation was used in either the fresh state or frozen (-70°C) then thawed.

The binding assay is performed manually using 96-well plates, or using a Biomek automated work station
30 (Beckman Instrument Co.). 3H -Nicotine was diluted in assay buffer to give a final concentration of 1.9 nM. The Biomek automated work station was programmed to automatically transfer 750 μ l of assay buffer with 3H -nicotine, 230 μ l of

membrane preparation and 20 μ l of solution containing the compound of interest in assay buffer, DMSO, ethanol:DMSO (1:1) or appropriate vehicle to the 96-well plate. Atropine was added to the incubation buffer at a final concentration of 3 μ M to block binding to muscarinic acetylcholine receptor sites. The plates were maintained on ice for 60 min and the tissue-bound radioactivity was separated from the free by rapid filtration in a Brandel Harvester onto GF/C filters presoaked in 0.5% polyethyleneimine for at least 2 hr. The filters were washed with 4x2 ml of ice-cold assay buffer and filters were transferred to vials to which 4 ml of scintillation cocktail was added. The radioactivity was measured in a LS-6500 Beckman Liquid Scintillation Counter in an auto-dpm mode. Data were analyzed by log-logit transformation or non-linear regression analysis (e.g., employing GraphPad Prism, available from GraphPad Software, San Diego, CA) to give IC_{50} values. Non-specific binding was defined by 10 μ M cytisine.

The ability of invention compounds to displace 3H -QNB (quinuclidinyl benzilate; 43 Ci/mmol) from muscarinic acetylcholine receptors in rat cerebral membranes was also tested using the above-described method in which 3H -nicotine was replaced with 60 pM 3H -QNB, and atropine was excluded from the incubation buffer.

The results of 3H -nicotine, 3H -cytisine and 3H -QNB binding/displacement assays of several invention compounds are summarized in Table I.

Table I
Displacement of Radiolabeled Ligands

Compound tested, Formula I, wherein...	IC ₅₀ (μM)		
	Nicotine	Cytisine	Quinuc Eenz
A = 4-hydroxyphenyl; B = absent; D = -S-; E = -CH ₂ CH ₂ -; G = 1-methylpyrrolidine	0.11	0.32	1.85
A = 4-aminophenyl; B = -CH ₂ CH ₂ CH ₂ -; D = -C(O)O-; E = -CH ₂ -; G = 1-methylpyrrolidine	0.082	0.19	0.6
A = 4-hydroxyphenyl; B = -CH ₂ CH ₂ -; D = -C(O)O-; E = -CH ₂ -; G = 1-methylpyrrolidine	0.075	0.22	>10
A = 3-fluoro-4-methoxyphenyl; B = absent; D = -S-; E = -CH ₂ CH ₂ -; G = 1-methylpyrrolidine	0.38	5.5	2.9
A = 2-chloro-4-hydroxyphenyl; B = absent; D = -S-; E = -CH ₂ CH ₂ -; G = 1-methylpyrrolidine	0.16	0.44	3.3
A = phenyl; B = -CH ₂ CH ₂ -; D = -C(O)O-; E = -CH ₂ -; G = 1-methylpyrrolidine	0.35	1.3	1.12

As evidenced by the IC₅₀ values in the Table, each of the compounds tested was able to displace acetylcholine receptor ligands from their binding sites in rat cerebral membranes.

Example 6
Neurotransmitter Release

Measurement of ^3H -dopamine (^3H -DA) release from rat striatal slices was performed according to the method of Sacaan et al., (*J. Pharmacol. Comp. Ther* 224:224-230 (1995)). Male Sprague-Dawley rats (250-300 g) were decapitated and the striata or olfactory tubercles dissected quickly on a cold glass surface. The tissue was chopped to a thickness of 300 μm with a McIlwain tissue chopper. After chopping again at right angles the tissue was dispersed and incubated for 10 min. at 37°C in oxygenated Krebs's buffer. ^3H -Dopamine (40 Ci/mmol, NEN-Dupont, Boston, Ma) was added (50 nM) and the tissue was incubated for 30 min. in Krebs's buffer containing 10 μM pargyline and 0.5 mM ascorbic acid. Aliquots of the minced tissue were then transferred to chambers of a Brandel Superfusion system in which the tissue was supported on Whatman GF/B filter discs. The tissue was then superfused with buffer at a constant flow rate of 0.3 ml/min by means of a Brandel peristaltic pump. The perfusate was collected in plastic scintillation vials in 3-min fractions, and the radioactivity was estimated by scintillation spectrophotometry. The superfusate for the first 120 min was discarded. After two baseline fractions had been collected, the superfusion buffer was switched to fresh buffer with or without compound of interest. At the end of the experiment the filter and the tissue were removed, and the radiolabeled neurotransmitter content was estimated after extraction into scintillation fluid. The fractional efflux of radiolabeled neurotransmitter was estimated as the amount of radioactivity in the perfusate fraction relative to the total amount in the tissue.

Following essentially the same procedure as set forth in the preceding paragraph, the amount of ^3H -norepinephrine (^3H -NE) released from rat hippocampus,

thalamus and prefrontal cortex slices superfused with buffer containing (or lacking) compounds of interest was also measured.

5 The results of studies of the effects of an invention compound (as compared to the effect of nicotine) on the release of neurotransmitters from rat brain slices are presented in Table II. The results presented in the Table are expressed as the percent fractional release.

Table II

Ligand-Stimulated Neurotransmitter Release Data

Ligand or Compound Tested, Formula I, wherein...	% of Nicotine Response ^a	
	³ H-DA [*] Striatum	³ H-NE [*] Hippocampus
Nicotine	100 (10 μ M)	100 (300 μ M)
A = 4-hydroxyphenyl; B = absent; D = -S-; E = -CH ₂ CH ₂ -; G = N-methyl-2-pyrrolidine	453	32
A = 3-fluoro-4-methoxyphenyl; B = absent; D = -S-; E = -CH ₂ CH ₂ -; G = N-methyl-2-pyrrolidine	21	n.d.
A = 2-chloro-4-hydroxyphenyl; B = absent; D = -S-; E = -CH ₂ CH ₂ -; G = N-methyl-2-pyrrolidine	800	n.d.
A = 4-hydroxyphenyl; B = absent; D = -S-; E = -CH ₂ CH ₂ CH ₂ -; G = R ¹ and R ² combine to form a 6-membered ring	225	12
A = 4-hydroxyphenyl; B = absent; D = -S-; E = -CH ₂ CH ₂ -; G = dimethylamino	165	n.d.
A = 4-hydroxyphenyl; B = absent; D = -S-; E = -CH ₂ -; G = N-methyl 7-azabicyclo- [2.2.1]heptane	660	n.d.
A = 4-hydroxyphenyl; B = absent; D = -S-; E = absent; G = N-methyl-4-piperidino	450	n.d.

- * DA = Dopamine;
 - NE = Norepinephrine
 - ^a Each compound was tested at 300 μ M
 - ^b n.d. = not determined
-

As shown in Table II, invention compound selectively induces release of catecholamines in different brain regions.

5

Example 7

Measurement of Acetylcholine Release in Rat Hippocampus

Male Sprague Dawley Rats (230-290 g) were anesthetized in a chamber saturated with isofluorane. Once immobilized, the rats were mounted in a Kopf stereotaxic apparatus with the incisor bar set at -3.3 mm (Praxinos and Watson, 1986). A midline incision was made on the skull to expose the underlying fascia. The skull was cleaned with an antibacterial preparation containing iodine and a hole was made in the skull at the following coordinates: AP, -3.5 mm and ML, +2.0 mm (Praxinos and Watson, 1986). A stainless steel guide cannula (Small Parts, Inc., Stillwater, FL) was cut to 2.0 mm length and inserted into the hole. Three additional holes were drilled into the skull surrounding the guide cannula and small machine screws were placed into these holes. The guide cannula and screws were secured by dental cement. A dummy cannula was inserted into the guide cannula to prevent clogging. The animals were removed from the stereotaxic frame and single housed for 3-7 days with free access to food and water.

25

On the day of the experiment, the rats were briefly anesthetized with isofluorane and the dummy cannulae were removed. A microdialysis cannula containing a Loop type probe with a rigid shaft and molecular weight cut-off of 6000 (ESA Inc, Chelmsfold, MA) of approximately 2 mm in length, was inserted into the guide cannula. Under

30

these conditions, the microdialysis probe extended 2 mm beneath the guide cannula. The animal was placed in plastic bowl (CMA 120; CMA Microdialysis, Acton, MA, USA) with a harness around the neck. The microdialysis probe was connected to a syringe pump through which a salt solution representing the ionic concentration of the cerebrospinal fluid (artificial CSF; 145 mM NaCl; 27 mM KCl; 10 mM MgCl₂ and 12 mM CaCl₂; pH 7.4; Moghaddam and Bunney, J. Neurochem, 53, 652-654, 1989) containing 100 nM neostigmine was pumped at a rate of 1.5 μ L/min.

Twenty minute fractions were collected and automatically injected via a sample loop and an auto-injector. The on-line microdialysis comprised of the following components: a CMA/100 microsyringe pump connected to a CMA/111 syringe selector. The mobile phase (100 mM disodium hydrogen phosphate; 2.0 mM 1-octane sulfonic acid sodium salt; 0.005% reagent MB (ESA Inc., Chelmsford, MA) pH 8.00 with phosphoric acid) was pumped using a model 580 ESA pump through a polymeric reverse phase column (ACH-3, ESA Inc., 3 μ M spherical particles; 3.2 mmx 15 cm). The effluent from the column was passed through an enzyme reactor containing immobilized acetylcholinesterase and choline oxidase (ACH-SPR, ESA Inc.). The HPLC column and the enzyme reactor were placed in a housing with a constant temperature of 35°C. Acetylcholine and choline in microdialysis samples were converted into hydrogen peroxide which was detected by amperometric oxidation in a ESA model 5041 analytical cell containing a glassy carbon target electrode and a palladium reference electrode. The oxidation potential was 250 mV and the signal was detected by a ESA model 5200 A Coulochem detector. The retention times for choline and acetylcholine under these conditions were 4 and 6 min, respectively. The limit of detection for acetylcholine was less than 100 fmol on column.

On the day of the experiment, 10-12 fractions were collected to establish the baseline acetylcholine release. Following the establishment of baseline, rats were injected with the test compound and samples were collected until the levels of acetylcholine in the dialysate samples returned to baseline levels (3-5 hr). Compounds were typically dissolved in saline and the pH of the solution was adjusted by the addition of NaOH. An example of the results that may be obtained are demonstrated in the data below in which rats were injected with a compound according to Formula Z wherein A = 4-hydroxyphenyl, B is not present, D = -S-, E = -CH₂CH₂-, and G = 1-methylpyrrolidino, at a dose of 40 mg/kg in a volume of 0.2 cc/rat.

The effects of various treatments on hippocampal acetylcholine receptors are shown in Table 1 and Figures 1-5. The attenuation of acetylcholine release by mecamylamine induced by a compound having Formula Z wherein A = 4-hydroxyphenyl, B = not present, D = -S-, E = -CH₂CH₂-, and G = 1-methylpyrrolidino, arguing for the involvement of nicotinic acetylcholine receptors in this response.

Table III

		Peak Increase, % of Baseline	Duration of Increase Above Baseline, (min.)
5	<u>Treatment</u>		
	Saline	220	20
	Nicotine	220	200
	Lobeline	400	200
10	Compound of Formula Z wherein: A = 4-hydroxyphenyl, B = not present, D = -S-, E = -CH ₂ CH ₂ -, and G = N-methyl-2-pyrrolidino	2,000	200
15	Compound of Formula Z wherein: A = 4-hydroxyphenyl, B = not present, D = -S-, E = -CH ₂ CH ₂ CH ₂ -, and G = R ^f and R ^g combine to form a 6-membered ring	1,000	100
20	Compound of Formula Z wherein: A = 4-hydroxyphenyl, B = not present, D = -S-, E = -CH ₂ CH ₂ -, and G = R ^f and R ^g combine to form a 6-membered ring	960	100
25	Compound of Formula Z wherein: A = 4-hydroxyphenyl, B = not present, D = -S-, E = -CH ₂ CH ₂ -, and G = R ^f and R ^g combine to form a 6-membered ring	817	100
30	Compound of Formula Z wherein: A = 4-hydroxyphenyl, B = -CH ₂ -, D = -S-, E = -CH ₂ CH ₂ -, and G = N-methyl-2-pyrrolidino		
35			
40			

The effects of invention compounds on locomotor activity of rats were evaluated using the procedure of O'Neill et al., *Psychopharmacology* 104:343-350 (1991).

This assay can be used to assess the primary effect of a compound on general motor activity. A decrease in locomotor activity is indicative of a possible sedative effect on the animal, whereas an increase in locomotor activity is indicative of a stimulant effect on the animal.

Locomotor activity of rats (male Sprague-Dawley (Harlan) weighing 200-250 gm) was measured for 2 hrs in photocell cages immediately after administration of the invention compound. Prior to the test day, the animals were placed in the activity cages for 3 hrs to familiarize them with the experimental environment. On the test day, the animals were placed in the photocell cages and then injected with compound 1.5 hrs later.

The photocell cages were standard rodent cages (30 cm x 20 cm x 40 cm) with four infrared beams crossing the long axis. The animals were under no motivational constraints and were free to move around. Movements from one infrared beam to another (ambulation) were called "crossover"; successive interruptions of the same beam (vertical and other movements such as grooming) were called "general activity."

The results of one such study are shown in Table IV. Results are reported as the percent of change from control values (i.e., saline injection) for two post-injection periods: 0 - 60 minutes and 60 - 120 minutes, respectively.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

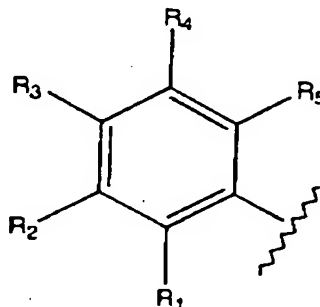
1. A compound having the Formula Z, as follows:



or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof

wherein:

A is



wherein:

each of R₁, R₂, R₃,

- 10 R₄ and R₅ are independently selected from hydrogen, halogen, cyano, cyanomethyl, nitro, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic, trifluoromethyl, pentafluoroethyl, -OR_A, -O-C(O)-R_A, -O-C(O)-N(R_A)₂, -SR_A, -NHC(O)R_A or -NHSO₂R_A, wherein R_A is selected from H, lower alkyl, substituted lower alkyl, aryl or substituted aryl, or -NR_BR_B, wherein
- 15 20 each R_B is independently selected from hydrogen or lower alkyl, and wherein at least one of R₁, R₂, R₃, R₄ or R₅ is not hydrogen;

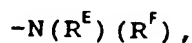
25 B is optionally present; with the proviso that when B is absent and D is -O-, at least one of R_1 , R_2 , R_3 , R_4 or R_5 is not hydrogen, and when B is present, B is selected from lower alkylene, substituted lower alkylene, cycloalkylene, substituted cycloalkylene, lower alkenylene, substituted lower alkenylene or lower alkynylene;

30 D is optionally present; and when present is selected from -O-, -C(O)-, -C(O)-NR_c-, -C(O)-O-, -O-C(O)-NR_c-, -S-, -S(O)-, -S(O)-NR_c-, -S(O)₂-, -S(O)₂-NR_c- or -S(O)=NH, wherein R_c is

35 selected from hydrogen, lower alkyl or substituted lower alkyl;

40 E is selected from lower alkylene, substituted lower alkylene, lower alkenylene, substituted lower alkenylene or lower alkynylene, with the proviso that when any one of R_1 , R_2 , R_3 , R_4 or R_5 is halogen, nitro, acetamido or cyano, and D is -O-, then E is not methylene;

G is a dialkylamino group having the structure:



45

wherein:

R^E is hydrogen or a lower alkyl, and

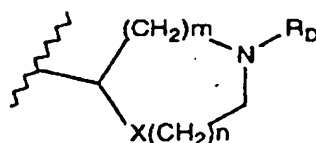
R^F is hydrogen or lower alkyl, or

R^E and R^F combine to form a 3-7 membered ring,

50

with the proviso that when G is dialkylamino, B is absent, D is -O-, and E is C₁₋₃ alkylene, then at least one of R^1 and R^5 is not alkyl, substituted alkyl, cycloalkyl or substituted cycloalkyl, or

55 G is a nitrogen-containing cyclic moiety having the structure:



as well as bicyclic-derivatives thereof,

wherein:

m is 0-2,

60 n is 0-3,

X is optionally present, and when present is selected from -O-, -CH₂O-, -S-, -CH₂S-, -S(O)-, -CH₂S(O)-, -S(O)₂-, -CH₂S(O)₂- or -CH₂N-, wherein n is not 0 when X is not present, and

65 R_D is selected from hydrogen, lower alkyl or lower cycloalkyl, or R_D is absent when the nitrogen atom to which it is attached participates in the formation of a double bond,

with the proviso that:

70 when B is not present, D is -O-, E is a C₁₋₃ alkylene, and G is a nitrogen-containing cyclic moiety wherein X is not present, then m and n combined ≠ 1; and

75 when B is not present, D is -S-, E is -CH₂CH₂-, G is a nitrogen-containing cyclic moiety wherein X is not present, m is zero, n is one and R_D is CH₃, and each of R₁, R₂, R₄

and R_5 is H, then R_3 is not H, Cl or tert-butyl; and

80 when B is not present, D is $-C(O)O-$, E is $-CH_2-$, and G is a nitrogen-containing cyclic moiety wherein X is not present, m is zero, n is one and R_0 is CH_3 , then at least one of R_1 , R_2 , R_3 , R_4 and R_5 is not H; and

85 when B is not present, D is $-C(O)-$, E is a C_{1-3} alkylene, and G is dialkylamino, then R^E and R^F combined are not $-(CH_2)_5-$; and

90 when B is not present, D is $-C(O)NR_c-$, E is $-CH_2CH_2-$, and G is a nitrogen-containing cyclic moiety wherein X is not present, m is zero, n is 3 and R_0 is hydrogen or lower alkyl, then R_1 is not alkoxy, when each of R_2 and R_5 is H, R_3 is NH_2 , and R_4 is halo.

2. A compound according to claim 1 wherein each of R_1 , R_2 , R_3 , R_4 and R_5 are independently selected from hydrogen, halogen, alkyl, substituted alkyl or $-OR_A$, wherein R_A is selected from H, lower alkyl or aryl.

3. A compound according to claim 1 wherein D is selected from $-O-$, $-C(O)-$, $-C(O)O-$ or $-S-$.

4. A compound according to claim 1 wherein G is an azetidino moiety or 1-methyl azetidino moiety.

5. A compound according to claim 1 wherein G is a piperidino moiety or 1-methylpiperidino moiety.

6. A compound according to claim 1 wherein A is selected from phenyl, 4-hydroxyphenyl, 4-aminophenyl, 2-chloro-4-hydroxyphenyl or 3-fluoro-4-methoxyphenyl.

7. A compound according to claim 1 wherein D is selected from $-C(O)O-$ or $-S-$.

8. A compound according to claim 1 wherein G is pyrrolidino wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

9. A compound according to claim 1 wherein:

A = 2-chloro-4-hydroxyphenyl,

B = not present,

D = -S-,

5

E = -CH₂CH₂-, and

G = pyrrolidino wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

10. A compound according to claim 1 wherein:

A = 3-fluoro-4-methoxyphenyl,

B = not present,

D = -S-,

5

E = -CH₂CH₂-, and

G = pyrrolidino wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

11. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl or 4-aminophenyl,

B = -CH₂CH₂- or -CH₂CH₂CH₂-,

D = -C(O)O-,

5

E = -CH₂-, and

G = pyrrolidino wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

12. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = $-\text{CH}_2\text{CH}_2-$,

D = $-\text{C}(\text{O})\text{O}-$,

E = $-\text{CH}_2-$, and

G = pyrrolidino wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

13. A compound according to claim 1 wherein:

A = phenyl,

B = $-\text{CH}_2\text{CH}_2-$,

D = $-\text{C}(\text{O})\text{O}-$,

E = $-\text{CH}_2-$, and

G = pyrrolidino wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

14. A compound according to claim 1 wherein:

A = 4-aminophenyl,

B = $-\text{CH}_2\text{CH}_2\text{CH}_2-$,

D = $-\text{C}(\text{O})\text{O}-$,

E = $-\text{CH}_2-$, and

G = pyrrolidino wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

15. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = not present,

D = $-\text{S}-$,

E = $-\text{CH}_2\text{CH}_2-$, and

G = pyrrolidino wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

16. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = $-\text{CH}_2-$,

D = $-\text{S}-$,

5

E = $-\text{CH}_2\text{CH}_2-$, and

G = pyrrolidino wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

17. A compound according to claim 1 wherein:

A = 2-fluoro-4-hydroxyphenyl,

B = not present,

D = $-\text{S}-$,

5

E = $-\text{CH}_2\text{CH}_2-$, and

G = pyrrolidino wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

18. A compound according to claim 1 wherein:

A = 4-($\text{NHSO}_2\text{-R}_A$)-phenyl, wherein R_A is $-\text{CH}_3$ or $-\text{CF}_3$,

B = not present,

5

D = $-\text{S}-$,

E = $-\text{CH}_2\text{CH}_2-$, and

G = pyrrolidino, wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

19. A compound according to claim 1 wherein:

A = 4-amino(toluenesulfonate)phenyl,

B = not present,

D = $-\text{S}-$,

5

E = $-\text{CH}_2\text{CH}_2-$, and

G = pyrrolidino, wherein X is not present, $n = 2$, $m = 0$ and R_0 is hydrogen or methyl.

20. A compound according to claim 1 wherein:

A = 2-methyl-4-hydroxyphenyl,

B = not present,

D = -S-,

E = -CH₂CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R_p is hydrogen or methyl.

21. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = not present,

D = -O-,

E = -CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R_p is hydrogen or lower alkyl.

22. A compound according to claim 1 wherein:

A = 4-(NHSO₂-R_A)-phenyl, wherein R_A is lower alkyl, aryl or -CF₃,

B = not present,

D = -O-,

E = -CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R_p is hydrogen or lower alkyl.

23. A compound according to claim 1 wherein:

A = 4-aminophenyl,

B = not present,

D = -O-,

E = -CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R_p is hydrogen or lower alkyl.

24. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = -CH₂-,

D = -O-,

5

E = -CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R₀ is hydrogen or lower alkyl.

25. A compound according to claim 1 wherein:

A = R-substituted phenyl, wherein R is defined the same as any one of R¹, R², R³, R⁴ or R⁵,

5

B = not present,

D = -S-,

E = -CH₂-, and

10

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R₀ is hydrogen or lower alkyl.

26. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = not present,

D = -S-,

5

E = -CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R₀ is hydrogen or lower alkyl.

27. A compound according to claim 1 wherein:

A = 4-methoxyphenyl,

B = -CH₂-,

D = -S-,

5

E = -CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R₀ is hydrogen or lower alkyl.

28. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = -CH₂-,

D = -S-,

E = -CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R₀ is hydrogen or lower alkyl.

29. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = not present,

D = -S-,

E = -CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R₀ is hydrogen or lower alkyl.

30. A compound according to claim 1 wherein:

A = 4-methylacetate phenyl,

B = not present,

D = -S-,

E = -CH₂CH₂-, and

G = pyrrolidino, wherein S is not present, n = 2, m = 0 and R₀ is hydrogen or lower alkyl.

31. A compound according to claim 1 wherein:

A = 4-carboxyphenyl,

B = not present,

D = -S-,

E = -CH₂CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R₀ is hydrogen or lower alkyl.

32. A compound according to claim 1 wherein:

A = 4-(O-C(O)-N(CH₃)₂)phenyl,

B = not present,

D = -S-,

E = -CH₂CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R₀ is hydrogen or lower alkyl.

33. A compound according to claim 1 wherein:

A = 4-(CH₂-NHSO₂-R_A)-phenyl, wherein R_A is lower alkyl, aryl or -CF₃,

B = not present,

D = -S-,

E = -CH₂CH₂-, and

G = pyrrolidino, wherein X is not present, n = 2, m = 0 and R₀ is hydrogen or lower alkyl.

34. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = not present,

D = -S-,

E = not present, and

G = 1-methyl-4-piperidino.

35. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = not present,

D = -S-,

E = -CH₂-, and

G = 7-azabicyclo[2.2.1]heptane or N-methyl 7-azabicyclo[2.2.1]-heptane.

36. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = not present,

D = -S-,

E = -CH₂-, and

G = 8-azabicyclo[3.2.1]octane or
N-methyl 8-azabicyclo[3.2.1]-
octane.

37. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = not present,

D = -S-,

E = -CH₂-, and

G = 1-azabicyclo[2.2.2]octane or
N-methyl 1-azabicyclo[2.2.2]-
octane.

38. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = not present,

D = -S-,

E = -CH₂-, and

G = 9-azabicyclo[4.2.1]nonane or
N-methyl 9-azabicyclo[4.2.1]-
nonane.

39. A compound according to claim 1 wherein:

A = 4-hydroxyphenyl,

B = not present,

D = -S-,

E = -CH₂CH₂CH₂-, and

G = dimethylamino.

40. A compound according to claim 1 wherein:

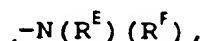
A = 4-hydroxyphenyl,

B = not present,

D = -S-,

E = $-(\text{CH}_2)_n-$, wherein $n = 1 - 6$, and

G = a dialkylamino group having the structure:



wherein:

R^{E} is hydrogen or a lower alkyl,
and

R^{F} is hydrogen or lower alkyl, or
 R^{E} and R^{F} combine to form a 3-7
membered ring.

41. A compound according to claim 1 wherein:

A = 4-(NH-SO₂-N(R_A)₂)phenyl, wherein R_A
is lower alkyl, aryl or -CF₃,

B = not present,

D = -S-,

E = -CH₂CH₂-, and

G = pyrrolidino, wherein X is not
present, $n = 2$, $m = 0$ and R₀ is
hydrogen or lower alkyl.

42. A method of modulating the activity of
acetylcholine receptors, said method comprising:

contacting cell-associated receptors with a
sufficient concentration of a compound according
to claim 1 to modulate the activity of said
acetylcholine receptors.

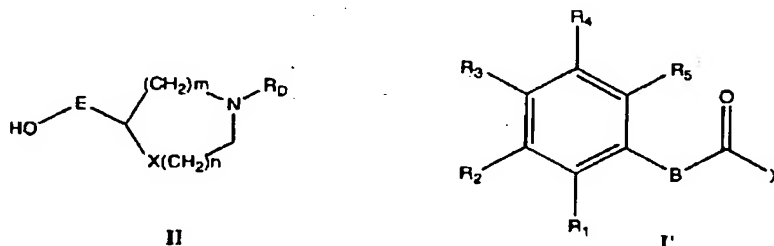
43. Method for treating Parkinson's disease, said method comprising administering a therapeutically effective amount of a compound according to claim 1 to a patient suffering from Parkinson's disease.

44. Method for treating Alzheimer's disease, said method comprising administering a therapeutically effective amount of a compound according to claim 1 to a patient suffering from Alzheimer's disease.

45. Method for treating dementia, said method comprising administering a therapeutically effective amount of a compound according to claim 1 to a patient suffering from dementia.

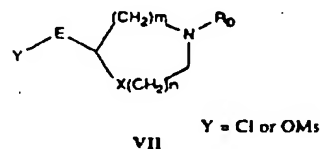
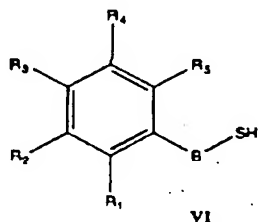
46. Method for controlling pain, said method comprising administering a therapeutically effective amount of a compound according to claim 1 to a patient suffering from pain.

47. A method for making compounds of structure Z according to claim 1, said method comprising contacting compound of Formula II with a compound of Formula I' under ester-forming conditions, wherein compounds II and I',
5 respectively, have the structures:



wherein X = halogen, OH or OZ, wherein Z = alkyl or maleimido.

48. A method for making compounds of structure Z according to claim 1, said method comprising contacting compound having Formula VI with compound having Formula VII under condensation conditions, wherein compounds VI and VII, respectively, have the structures:



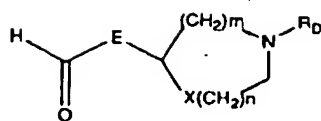
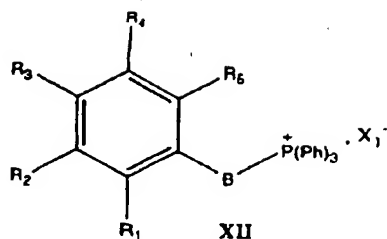
49. A method according to claim 48 further comprising oxidizing the initial condensation product to produce a sulfone derivative thereof.

50. A method according to claim 48 further comprising oxidizing the initial condensation product to produce a sulfoxide derivative thereof.

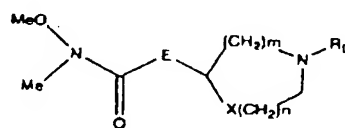
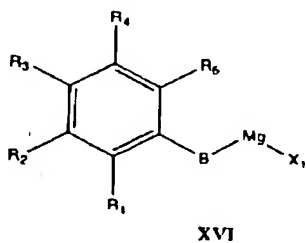
51. A method for making compounds of structure Z according to claim 1, said method comprising:

condensing aldehyde XIII with phosphonium salt XII under Wittig reaction conditions, and thereafter optionally reducing the resulting double bond, wherein XII and XIII have the structures

66



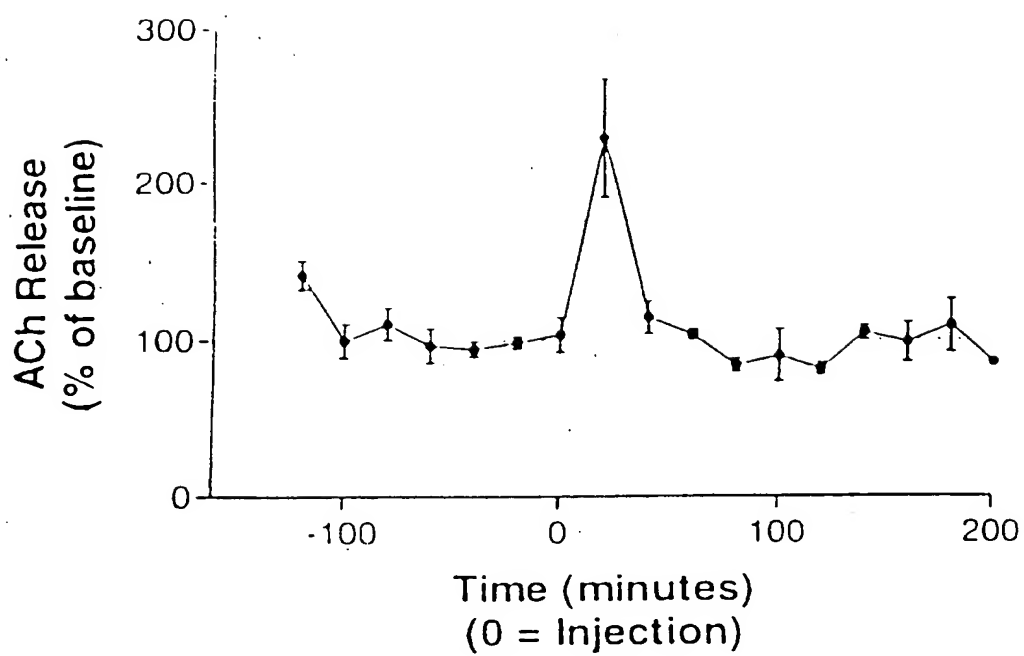
52. A method for making compounds of structure Z according to claim 1, said method comprising contacting Grignard reagent XVI with compound XVII under condensation conditions, wherein XVI and XVII have the structures:



5

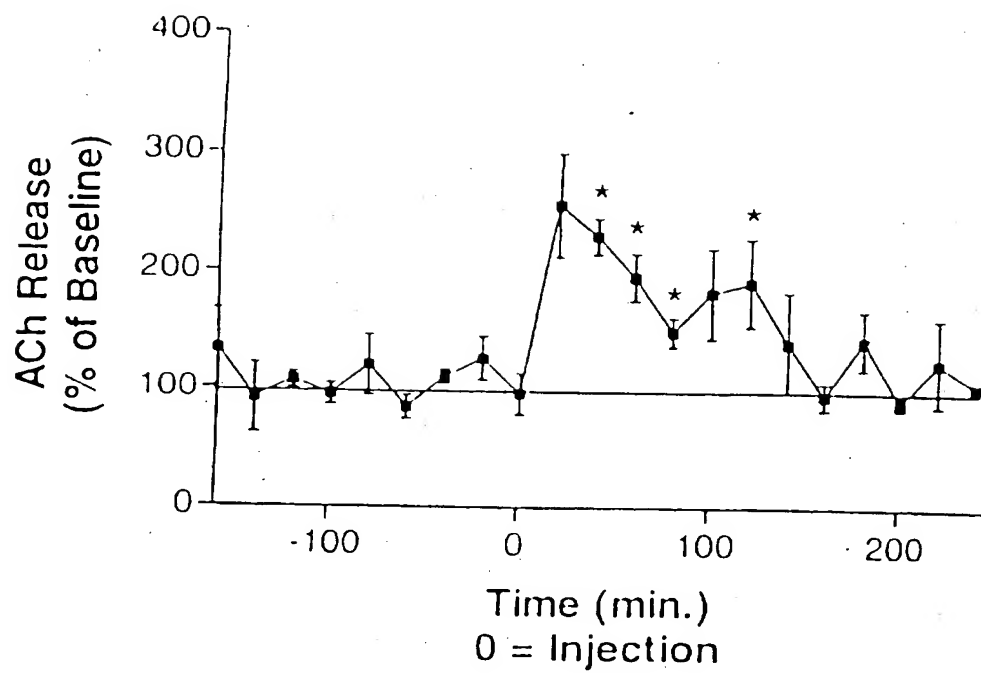
53. A method according to claim 52 wherein amide XVII is prepared by a Wittig-Horner reaction of aldehyde XIX with $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, followed by hydrogenation and amidation.

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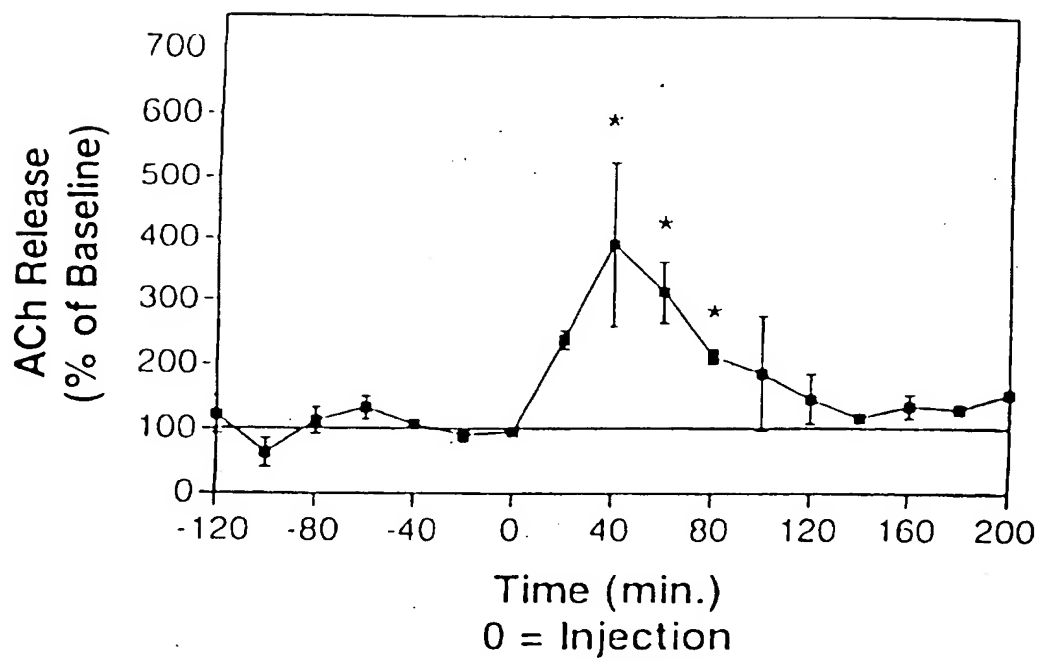
FIGURE 1

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FIGURE 2

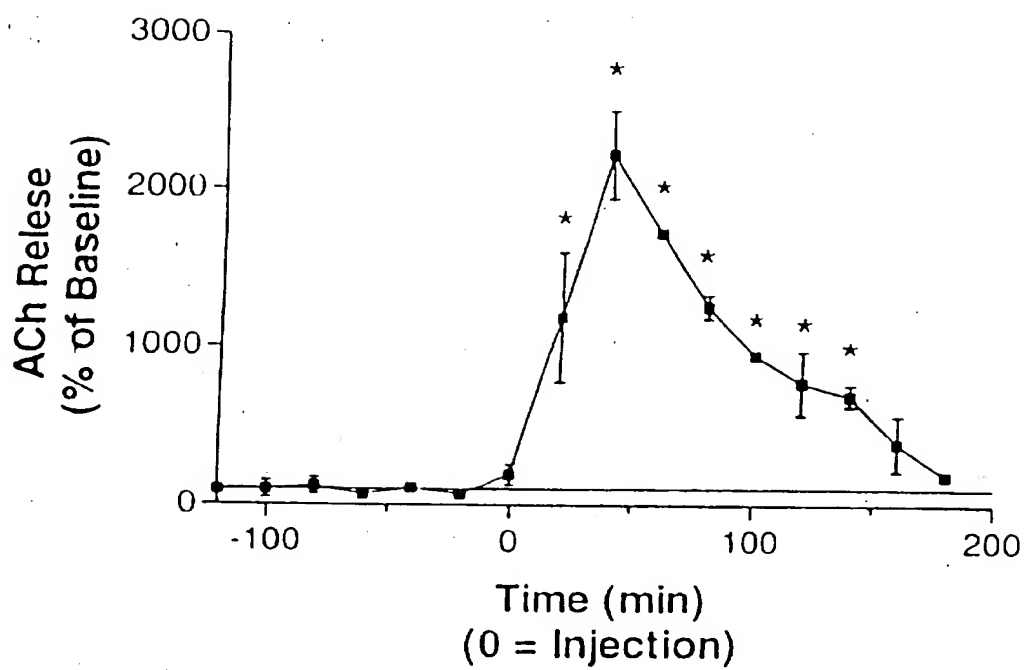


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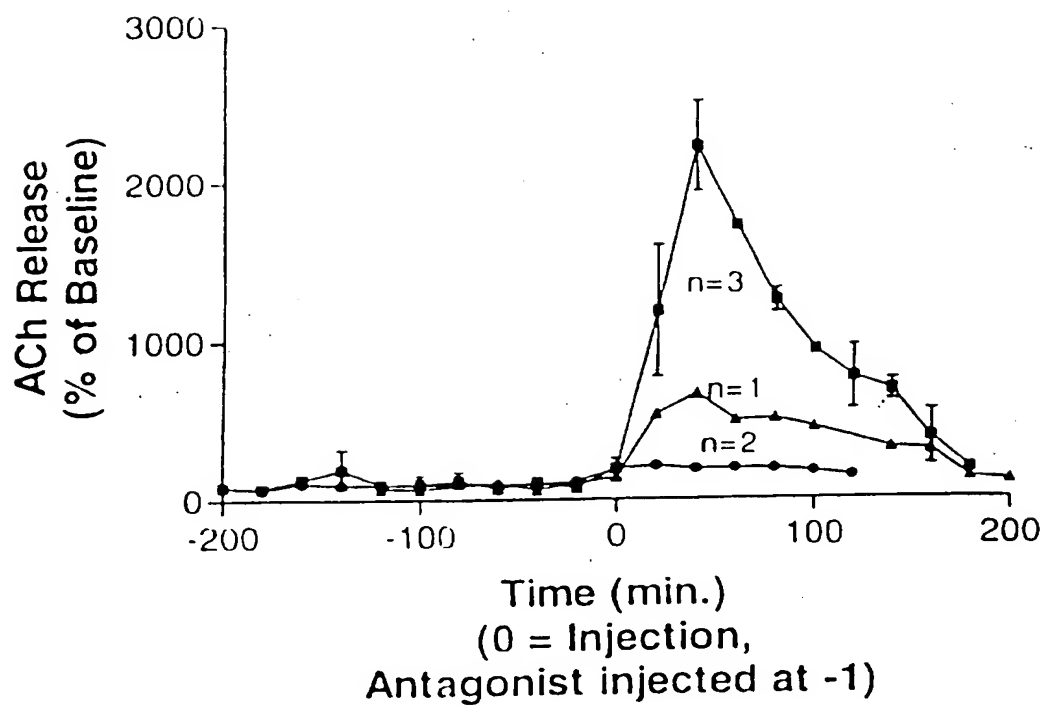
FIGURE 3

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FIGURE 4



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FIGURE 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/18569

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/08 C07D207/12 C07D209/94 C07D211/54 C07D401/02
A61K31/40 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BIOORG. MED. CHEM. LETT. (1996), 6(19), 2283-2288 CODEN: BMCLE8;ISSN: 0960-894X, 1996, XP000618280 ELLIOTT, RICHARD L. ET AL: "2-(Aryloxymethyl) azacyclic analogs as novel nicotinic acetylcholine receptor (nAChR) ligands" see the whole document ---	1-53
X	J. ENVIRON. SCI. HEALTH, PART B (1983), B18(4-5), 515-27 CODEN: JPFCO2;ISSN: 0360-1234, 1983, XP000618288 KASZUBSKA, J. ET AL: "Fungicidal activity of 2-[2-(arylthio)ethyl]pyrrolidine derivatives" see the whole document ---	1-3,7,8
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

20 February 1997

Date of mailing of the international search report

0 3. 03. 97

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Kissler, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/18569

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	POL. J. CHEM. (1981), 55(7-8), 1681-4 CODEN: PJCHDQ, 1981, XP000618279 BAL, STANISLAW ET AL: "Synthesis of 1-acyl-2-[2-(S-arylthio)ethyl]pyrrolidines " see the whole document ---	1-3,7,8
X	POL. J. CHEM. (1982), 56(10-12), 1543-7 CODEN: PJCHDQ, 1982, XP000618493 KASZUBSKA, JANINA ET AL: "Synthesis of derivatives of 2-[2-(arylthio)ethyl]pyrrolidine" see table 1 ---	1-3,7,8
A	WO 94 07489 A (SALK INSTITUTE) 14 April 1994 see the whole document ---	1-46
P,X	US 5 472 958 A (D. E. GUNN ET. AL.) 5 December 1995 see the whole document ---	1-53
A	US 4 721 783 A (UNITED PHARMACEUTICALS) 26 January 1988 see the whole document ---	1-46
P,A	WO 96 11931 A (SALK INSTITUTE) 25 April 1996 see the whole document -----	1-46

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/18569

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 43-46 are directed to a method of treatment of (diagnostic method practised on) the human/animal body (Art. 52(4) EPC) the search has been carried out and based on the alleged effects of the compound/ composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims searched completely: 9-15, 17-20, 25, 26, 29-33, 41
Claims searched incompletely: 1-8, 16, 21-24, 27-28, 34-40, 42-53
see attached sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The generic formula Z contains almost no fixed structural moiety. In addition, the large number of values for most of the variables, in conjunction with their cascading meanings and numerous provisos, renders the scope of the invention for which protection is sought ill-defined and obscure. Consequently, a complete search is precluded for practical and economic reasons.

Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the following case(s):

Generic structure covering the examples provided in the descriptive part of the application:

1. A= opt. subst. phenyl, B=(CH₂)₂₋₃, D= O=C-O, E=CH₂, G= pyrrolidinyl-2
2. A= subst. phenyl, B=bond, D=S, E= (CH₂)₁₋₃, G= pyrrolidinyl-2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/18569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9407489	14-04-94	NONE	
US-A-5472958	05-12-95	NONE	
US-A-4721783	26-01-88	US-A- 4857535	15-08-89
		US-E- RE33907	28-04-92
WO-A-9611931	25-04-96	US-A- 5567710	22-10-96
		AU-A- 3828095	06-05-96

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